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TAMPERE UNIVERSITY OF TECHNOLOGY

TATU RIMPILÄINEN
AEROBIC OXIDATION OF LITHIATED 1,3-DITHIANES AND
DITHIOACETALS

Master of Science thesis

Examiners:

Adj. Prof. Nuno R. Candeias

M.Sc. João R. Vale

Examiners and topic approved by the
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ABSTRACT

TATU RIMPILÄINEN: Aerobic Oxidation of Lithiated 1,3-Dithianes and Dithioacetals
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Lithiated compounds are well known to be reactive towards oxygen. The initial studies conducted at Tampere University of Technology had shown that upon exposure of 2-aryl-2-lithio-1,3-dithianes to air, three equivalents of 1,3-dithianes undergo an autooxidative condensation forming previously unreported products in good yields. Since only cyclic 2-aryl-1,3-dithianes were previously studied, the objective of this thesis was to study whether the scope of the oxidation reaction could be extended to acyclic lithiated benzaldehyde dithioacetals and 2-alkyl-1,3-dithianes. The study was performed by preparing the dithioacetals and 1,3-dithianes and then oxidizing the lithiated substrates. The results of the oxidation reactions were evaluated by determining the structures of isolated products by using NMR and mass spectrometry and then comparing the relative yields of the products.

The aerobic oxidations of lithiated benzaldehyde dithioacetals derived from primary, secondary and benzene thiols yielded α -sulfide ketones and orthothioesters. The observed products were analogous to the products obtained from the oxidations of 2-aryl-2-lithio-1,3-dithianes, which indicated that the same autooxidative condensation mechanism operated. When lithiated *n*-butylthiol dithioacetal was oxidized, an excellent 97% yield of α -sulfide ketone and 72% yield of orthothioester was obtained. When dithioacetals derived from secondary or benzene thiols were used, the observed yields decreased significantly, which was likely due to increased steric hindrance. The oxidation of *tert*-butylthiol dithioacetal afforded a thioester in 62% yield, which suggested that the oxidation mechanism proceeds by forming an initial thioester intermediate. Bulky *tert*-butyl probably prevented further condensations from occurring. Dithioacetal derived from benzylic thiol was observed to form an unexpected product upon treatment with *n*-butyllithium. This could be a result of an anionic rearrangement, however, further studies are required to confirm the observation.

Oxidations of 2-alkyl-2-lithio-1,3-dithianes afforded 1,2-diketone derivatives where the other carbonyl was still protected as a 1,3-dithiane. While the yields of the derivatives were poor, the observed structures provided more information about the mechanism of the oxidation. It is likely that the obtained products resulted from an attack of excess lithiated 1,3-dithiane to the thioester intermediate. In contrast to 2-aryl-1,3-dithiane, the reaction halted after the first condensation because the formation of a lithium enolate likely competed with the second condensation. As with *tert*-butylthiol dithioacetal, the oxidation of lithiated 2-*tert*-butyl-1,3-dithiane was observed to halt at the thioester intermediate, which was likely due to similar steric reasons. Despite the high value of 1,3-dithianes in synthetic chemistry, the work described herein presents an insight into one of the main limitations in using of 2-lithio-1,3-dithianes, namely previously reported inconsistent yields and formation of byproducts.

TIIVISTELMÄ

TATU RIMPILÄINEN: Litium 1,3-ditiaanien ja ditioasetaalien aerobinen hapetus
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Alkyyllitiumyhdisteet ovat tunnetusti erittäin reaktiivisia hapen kanssa. Alustavat tutkimukset Tampereen Teknillisessä Yliopistossa osoittivat, että kun 2-aryyli-2-litium-1,3-ditiaanit reagoivat ilman kanssa, kolme ekvivalenttia 1,3-ditiaaneja kondensoituu hapetuen. Tuotteena saatiin tällöin aikaisemmin kirjallisuudessa tuntemattomia yhdisteitä hyvillä saannoilla. Koska nämä aikaisemmat tutkimukset tehtiin vain syklisillä 2-aryyli-1,3-ditiaaneilla, oli tämän diplomityön tehtävänä selvittää, voitaisiinko hapetusreaktiota soveltaa myös asyklisiin, bentsaldehydistä johdettuihin litium ditioasetaaleihin. Tutkimuksessa valmistettiin ja hapetettiin ditioasetaaleja sekä 1,3-ditiaaneja. Hapetuksen tuloksia arvioitiin määrittämällä reaktiotuotteiden rakenteet NMR- ja massaspektroskopiolla sekä vertaamalla tuotteiden suhteellisia saantoja keskenään.

Primaarisesta ja sekundaarisesta tiolista sekä bentseenitiolista johdettujen bentsaldehydin ditioasetaalien hapetus tuotti α -sulfidiketoneja sekä ortotioestereitä. Tuotteet olivat samankaltaisia aikasemmin 2-aryyli-2-litium-1,3-ditiaanien hapetuksista saatujen tuotteiden kanssa, joka viittasi siihen, että hapetuksen mekanismi oli sama kummassakin tapauksessa. Kun *n*-butyylioliolista johdettu litium ditioasetaali hapetettiin, α -sulfidiketonin saanto oli erinomainen 97 % ja ortotioesterin vastaavasti 72 %. Sekundaarisen ja bentseenitiolin tapauksissa saannot laskivat merkittävästi. Tämä johtui todennäköisesti steerisistä tekijöistä. *Tert*-butyylioliolista johdettu ditioasetaali tuotti hapetuksessa tioesterin 62 % saannolla, joka viittaa siihen, että reaktiossa muodostuu aluksi välituotteena tioesteriä. Suurikokoinen *tert*-butyyliiryhmä todennäköisesti esti reaktion etenemisen tätä välituotetta pidemmälle. Kun bentsyylioliolista johdetut ditioasetaalit reagoivat *n*-butyyllitiumin kanssa, muodostui odottamaton tuote. Tämä saattoi johtua anionisesta toisiintumisesta, mutta havainnon vahvistaminen vaatii vielä lisää tutkimuksia.

2-alkyyli-2-litium-1,3-ditiaanien hapetuksesta saatiin tuotteeksi 1,2-diketonijohdannaisia, joiden toinen karbonyyliiryhmä oli edelleen suojattu 1,3-ditiaaniksi. Vaikka näiden tuotteiden saannot jäivät heikoiksi, niin niiden rakenteet antoivat lisää tietoa hapetuksen mekaniismista. Reaktiosta saadut tuotteet todennäköisesti syntyivät hapettumattoman 2-litium-1,3-ditiaanin reagoitessa tioesterivälituotteen kanssa. Toisin kuin 2-aryyli-2-litium-1,3-ditiaanien tapauksessa, reaktio pysähtyi ensimmäisen kondensaation jälkeen, koska litium enolaatin muodostuminen todennäköisesti esti toisen kondensaation tapahtumisen. Samoin kuin *tert*-butyylioliolista johdetun ditioasetaalin tapauksessa, 2-litium-2-*tert*-butyyli-1,3-ditiaanin hapettuminen pystähtyi tioesterivälituotteeseen. Tämä johtui todennäköisesti samankaltaisista steerisistä syistä. Huolimatta 1,3-ditiaanien käyttökelpoisuudesta synteettisessä kemiassa, tässä työssä kuvatut reaktiot antavat syvemmän kuvan niistä rajoituksista, jotka liittyvät 2-litium-1,3-ditiaanien käyttöön, kuten aikaisemmin raportoidut vaihtelevat saannot ja sivutuotteiden muodostuminen.

PREFACE

This Master of Science thesis was done in the Laboratory of Chemistry and Bioengineering at Tampere University of Technology. The experimental part of the thesis was done between June and September 2017.

I am grateful to my examiner Adjunct Professor Nuno R. Candeias for the topic of the thesis and for all the support he has provided. I am also thankful for my second examiner, Master of Science João R. Vale who helped me with the thesis and gave me valuable practical advice during the experimental work. I also thank Doctor of Philosophy Alexander Efimov for the help with mass spectrometry.

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Tatu Rimpiläinen

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LIST OF ABBREVIATIONS AND SYMBOLS

^{13}C	carbon-13
^1H	proton
6-31G(d)	Pople basis set
δ	chemical shift (ppm)
d	doublet
DBH	1,3-dibromo-5,5-dimethylhydantoin
DCE	1,2-dichloroethane
DFT	density functional theory
ESI	electrospray ionization
Et	ethyl
EtOAc	ethyl acetate
equiv.	molar equivalent
HMPA	hexamethylphosphoramide
HR-MS	high-resolution mass spectrometry
<i>i</i> -Pr	<i>iso</i> -propyl group
J	coupling constant
MP2(fc)	second order Møller Plesset perturbation theory (frozen core)
m	multiplet (NMR spectra)
n_{C}	non-bonding orbital of carbon
<i>n</i> -Bu	<i>n</i> -butyl group
<i>n</i> -BuLi	<i>n</i> -butyllithium
NBS	<i>N</i> -bromosuccinimide
NiCRA	nickel containing complex reducing agent
NMR	nuclear magnetic resonance
Pr	propyl
r.t.	room temperature
$\sigma_{\text{S-C}}^*$	anti-bonding orbital of sulfur-carbon σ -bond
s	singlet
<i>sec</i> -Bu	secondary butyl group
$\text{S}_{\text{N}}2$	bimolecular nucleophilic substitution
TABCO	2,4,4,6-tetrabromo-2,5-cyclohexadienone
TBDMSO	<i>tert</i> -butyldimethylsilyloxy group
<i>tert</i> -Bu	tertiary butyl group
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
t	triplet

1. INTRODUCTION

Organosulfur chemistry is a very diverse area of the organic chemistry and therefore it is no surprise that numerous important reactions in modern organic chemistry have arisen from this particular field of research [1–4]. A case in point and the central focus of this thesis are two simple cases of organosulfur compounds, dithioacetals and 1,3-dithianes. Since the first reports by Corey and Seebach on using lithiated 1,3-dithianes as synthetically valuable acyl anion equivalents an extensive amount of research on this specific area of organosulfur chemistry has been published [5, 6]. The usefulness of this strategy has led to many applications especially in the synthesis of natural products [7, 8]. While dithioacetals have gathered less attention than 1,3-dithianes, the chemistry of the two organosulfur compounds are nevertheless closely related [9].

The use of dithioacetals and 1,3-dithianes as acyl anion equivalents is enabled by the ability sulfur groups to stabilize carbanions bonded to sulfur-groups [10–13]. This property makes the protons on alpha carbon acidic enough to be deprotonated by alkyllithium base. The resulting lithiated dithioacetals and 1,3-dithianes can then be reacted with various electrophiles. However, due to the well-known reactivity of alkyllithium compounds towards oxygen and moisture the handling of the compounds should be done strictly under inert atmosphere [14, 15]. A couple of cautionary examples of unintended oxidations of lithiated 1,3-dithianes have been published. The oxidations were reported to proceed through a thioester intermediate, which is then attacked by excess lithiated 1,3-dithiane resulting in an alcohol. [16, 17]

Formation of similar alcohols has also been attempted by double addition of lithiated 2-alkyl-1,3-dithianes to carboxylic acid derivatives by Valiulin *et al.* [18]. The attempt was reported to be unsuccessful if 2-substituents longer than methyl were used due to an unexpected 1,3-dithiane ring opening after the first addition. Considering the previous report on formation of thioester intermediates by oxidation of 2-lithio-1,3-dithianes and the report on double addition 2-lithio-1,3-dithianes to carboxylic acid derivatives, it was envisioned that these two reactions could be combined. The idea entails that the *in situ* formed thioester intermediate would act as an electrophile similarly to the carboxylic acid derivatives. Initial experiments done by my colleague verified that thioesters could indeed work similarly to carboxylic acid derivatives and that the *in situ* formation of the thioester

intermediate by aerobic oxidation of lithiated 2-aryl-1,3-dithianes would lead to similar ring-opened products that Valiulin *et al.* reported previously. [19]

Since only cyclic 2-aryl-1,3-dithianes were initially used in the oxidation experiments by my colleague, the aim of this thesis was to study whether the scope of the oxidations could be extended to acyclic dithioacetals derived from benzaldehyde and 2-alkyl-1,3-dithianes. It was envisioned that if the oxidation reaction of lithiated acyclic dithioacetals worked similarly to the oxidation of lithiated cyclic 2-aryl-1,3-dithianes, novel α -sulfide ketones and orthothioesters would be obtained as products. The study was performed by preparing the dithioacetals and 1,3-dithianes using modified procedures from literature and then oxidizing the lithiated substrates with air or pure oxygen. The scope of the oxidation reaction was then evaluated by isolating the products and by determining the structure and relative yield of each isolated product. The determination of the structures was done by using NMR and mass spectroscopy.

The second chapter of the thesis will discuss about the chemistry of dithioacetals and 1,3-dithianes. The structure and reactivity of the compounds will be explained in the terms of sulfur chemistry. In addition, the chapter introduces methods of preparing dithioacetals and 1,3-dithianes and probably the most common reaction where lithiated 1,3-dithianes are used, namely Corey–Seebach reaction. The third chapter explores some of the previously reported reactions of lithiated 1,3-dithianes with oxygen as a background for the experimental part the thesis. The chapter also introduces the initial work that led to the studies done in this thesis. The fourth chapter presents the results obtained from the experimental part of the thesis and the fifth chapter will summarize those results. Synthesis methods and characterization data of the compounds made during the thesis are presented in the last chapter. Finally, the NMR spectra of the characterized compounds are presented in the appendices. It should be noted that the naming of the compounds in the thesis is not consistently following the IUPAC recommendations to keep the names of the compounds more compact and legible.

2. DITHIOACETALS AND 1,3-DITHIANES

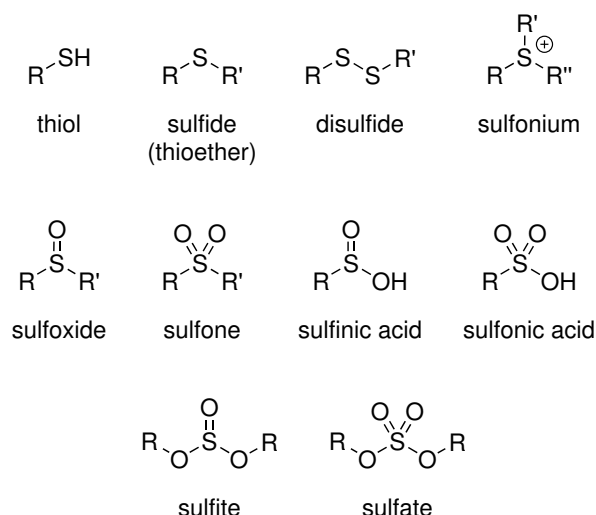
As sulfur is just one row below oxygen in the periodic table both atoms share the same number of valence shell electrons making the chemistries of sulfur and oxygen somewhat similar. However, there are some substantial differences which make sulfur quite different from oxygen in terms of organic reactions.

Sulfur is significantly less electronegative than oxygen. In commonly used electronegativity scales, when scaled to the original Pauling range, the electronegativity value of sulfur varies between 2.4–2.7 and the electronegativity of oxygen varies between 3.4–3.6. For comparison, carbon electronegativity is analogously calculated to be between 2.5–2.6, which is very close to electronegativity of sulfur. [20]

In carbon–oxygen bond the differences in electronegativities between the atoms causes the carbon to have partial positive charge and oxygen to have partial negative charge, whereas in sulfur–carbon bonds differences in electronegativities are less pronounced and the bond is not as polarized. This decreases the ionic character of organosulfur compounds compared to their oxygen analogs. This in turn decreases the importance of hydrogen bonding in sulfur compounds. [1, 3, 21]

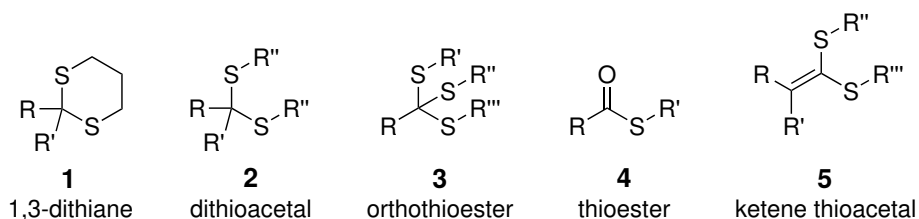
The sulfur atom is also larger than oxygen atom, covalent radii of oxygen is 70.2 pm and sulfur is 104.9 pm. This causes sulfur to form weaker σ bonds and to have weaker π bond interaction with neighboring atoms. Weaker bonds also mean that sulfur-carbon σ and π bonds have lower dissociation energies than respective oxygen bonds. As a consequence of larger size, sulfur is more polarizable than oxygen, which makes thiols more acidic than alcohols. Despite the greater acidity, the lone pairs on sulfur are more nucleophilic than the lone pairs on oxygen. [1, 3, 21]

Although sulfur and oxygen atoms have the same valence shell configuration, sulfur can extend its valency unlike oxygen. This is possible because lone pairs on sulfur can participate in bonding. While this is an interesting and challenging topic, the more detailed theory behind the ability of sulfur and other third row elements to extend their valency is out of scope of this thesis. [22, 23] Nevertheless, the ability of sulfur to extend its valency leads to a surplus of functional groups in organosulfur chemistry. Scheme 2.1 lists some of the more common sulfur containing moieties in organosulfur compounds. [1, 24]



Scheme 2.1 Common sulfur containing moieties [1, 24].

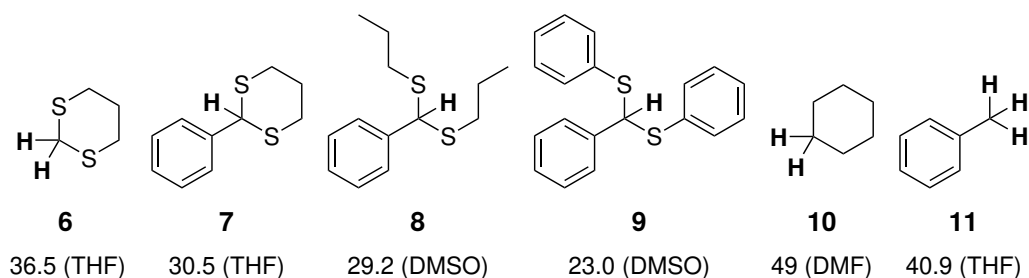
This thesis concentrates on compounds with divalent sulfur, namely the ones presented in Scheme 2.2. This chapter will discuss about the chemistry of the first two, 1,3-dithiane **1** and dithioacetal **2**, as those are used in the experimental section of thesis. In addition, dithianes are widely used in modern organic synthesis as will be discussed in Section 2.3. Compounds that have a carbon with geminal sulfide groups, such as 1,3-dithianes **1** and dithioacetals **2** are commonly called *S,S*-acetals in this thesis when there is no need to draw a distinction. In addition, orthothioesters **3**, thioesters **4** and ketene thioacetals **5** are mentioned in this chapter and in the later, experimental part of the thesis.



Scheme 2.2 Sulfur containing compounds discussed in the thesis

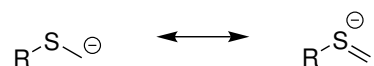
2.1 Structure and Reactivity

Sulfur is well known to enhance the acidity of protons on the α -carbons. The pK_a value of 1,3-dithiane **6** in THF has been reported to be 36.5 and for 2-phenyl-1,3-dithiane **7** reported value is 30.5 [25]. The same applies to dithioacetals, for example (phenylmethylene)-bis(propylsulfane) **8** has estimated pK_a of 29.2 in DMSO and (phenylmethylene)bis(phenylsulfane) **9** has pK_a of 23.0 [26]. For comparison, cyclohexane **10** has been estimated to have pK_a of 49 in DMF and toluene **11** has been estimated to have pK_a of 40.9 in THF [27, 28]. Acidic protons in the structures are presented in Scheme 2.3. Generally, this acidifying effect is attributed to anion stabilization ability of sulfur.

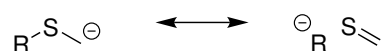


Scheme 2.3 Acidic protons in structures containing sulfur groups and reported pK_a values in solvent phase [25–28].

Anion stabilization by sulfur groups has been explained to occur by three mechanisms. Originally stabilization was thought to involve d-orbitals of sulfur. This stabilization mechanism implies resonance donation of carbanion 2p lone pair to sulfur 3d orbitals (Scheme 2.4). [26, 29] However, the d-p π -bonding mechanism is no longer strongly supported by evidence [10, 30]. Second suggested stabilization mechanism involves negative hyperconjugation, *i.e.*, $n_C \rightarrow \sigma_{S-C}^*$ donation, which can be presented by a double bond–no bond resonance structures (Scheme 2.5) [11–13]. Finally, stabilization of carbanion is also attributed to polarizability of sulfur [10].



Scheme 2.4 Resonance stabilization of carbanion 2p lone pair to sulfur 3d orbitals. [10]



Scheme 2.5 Lewis structure presentation of negative hyperconjugation. The presentation is not realistic as in actuality $S-R$ bond does not break, but only elongates. In addition, $S-C^-$ bond shortens and rotational barrier of the bond decreases in computational models. [11–13]

Which mechanism then contributes the most to the carbanion stabilization ability of sulfur? *Ab initio* calculations by Wiberg and Castejon [11] and a DFT study by Cuevas and Juaristi [12] both suggest that the negative hyperconjugation has a significant effect in stabilizing the anion. Furthermore, Süveges and Podlech reported in their recent computational study [13], that $n_C \rightarrow \sigma_{S-C}^*$ interaction energy in cyclohexyl methyl sulfide α -carbanion equals 91.2 kJ/mol; this applies only to the most stable conformation where $S-Me$ bond is antiperiplanar to lone pair on carbon, whereas the interaction energy quickly decreases as the dihedral angle changes.

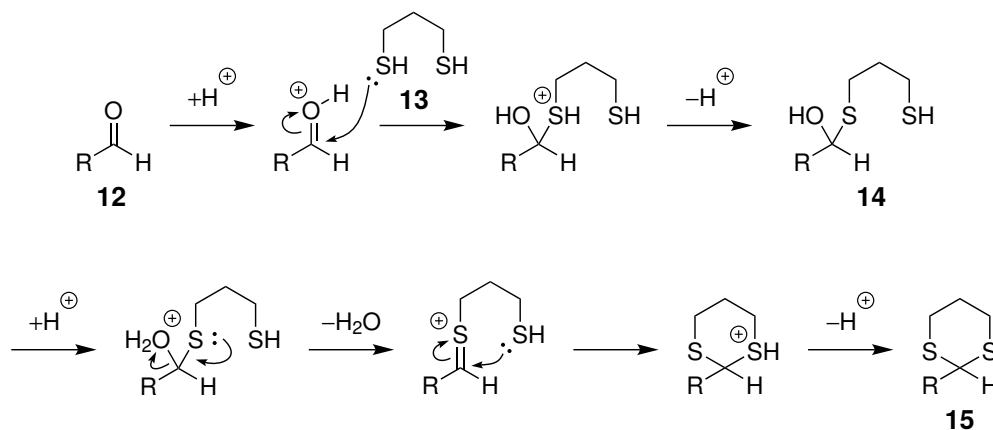
However, an experimental study by Bernasconi and Kitteridge [10] on intrinsic rate constants of deprotonation of (phenylthio)nitromethane indicates that sulfur polarizability is the dominant anion stabilizing factor. They base their result on the fact that sulfur polarizability strongly stabilizes the transition state, whereas d-p bonding and negative hyperconjugation only stabilize the transition state weakly compared to the carbanion. Therefore, accord-

ing to Bernasconi *et al.*, significantly increased intrinsic rate constant of deprotonation induced by adding a phenylthio group proves that polarization is the main operating mechanism. They also point out that while the previous results by Wiberg *et al.* [11] and Cuevas *et al.* [12] suggest that negative hyperconjugation is a significant mechanism, it does not necessarily prove that it is a dominant factor. The same argument can be applied to later study by Süveges *et al.* [13]. Whatever the mechanism of the carbanion stabilization may be, it is clear that sulfur increases the acidity of alpha carbons. This property is exploited in Corey-Seebach reactions as will be discussed later in Section 2.3.

Before the reactions of sulfur stabilized carbanions are discussed, the synthesis of dithioacetals and 1,3-dithianes is introduced as those are commonly used in the reactions such as Corey-Seebach, which require carbanion stabilization. In addition, dithioacetals and 1,3-dithianes were used in the experimental part of the thesis and the next section will provide the necessary background theory for the later discussion about the results in Chapter 4.

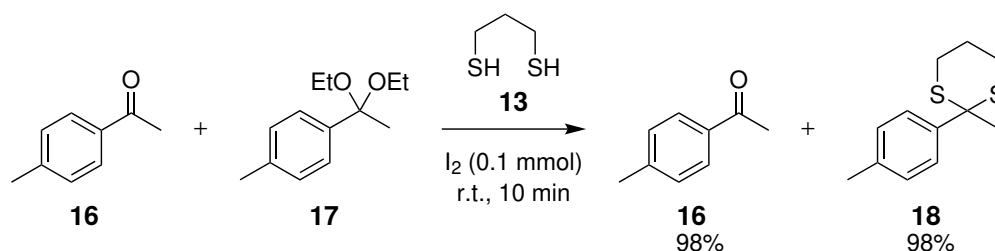
2.2 Preparation of Dithioacetals and 1,3-Dithianes

In general, *S,S*-acetals are prepared by condensation reaction of a carbonyl compound and a thiol in the presence of protic or Lewis acid [31]. If thiol is used, the product is acyclic dithioacetal **2**, whereas propane-1,3-dithiol will afford cyclic 1,3-dithiane **1**. Analogously, ethane-1,2-dithiol can be used to form the five ring 1,3-dithiolane ($RR'C(SCH_2CH_2S)$). However, 2-H-1,3-dithiolanes are known to cleave upon treatment with an alkyl lithium base, which limits their use compared to other *S,S*-acetals [32]. The mechanism is same as in *O,O*-acetal formation and the reaction is also called thioacetalization [33]. Scheme 2.6 presents the mechanism for Brønsted acid catalyzed formation of 1,3-dithiane **15** from an aldehyde **12** and propane-1,3-dithiol **13**. The first step is acid catalyzed addition of thiol to aldehyde to afford hemithioacetal intermediate **14**, which then loses water to form the 1,3-dithiane. The mechanism is the same for dithioacetals. [34, 35]



Scheme 2.6 Thioacetalization of aldehyde with propane-1,3-dithiol. [33–35]

Instead of aldehydes and ketones, *S,S*-acetals can be also made by transthioacetalizing masked aldehydes such as *O,O*-acetals and *O,S*-acetals. The reaction is typically conducted by using the same catalysts and reaction conditions as when thioacetalizing aldehydes and ketones. In some cases transthioacetalization can be advantageous compared to thioacetalization as it enables chemoselective conversion of *O,O*-acetals into *S,S*-acetals in the presence of ketones if mild enough catalyst is used. For example, Firouzabadi *et al.* [36] reported that diethyl acetal of 4-methyl acetophenone **17** could be transthioacetalized to yield dithiane **18** almost quantitatively in the presence of the parent ketone **16** when iodine was used as a catalyst (Scheme 2.7).



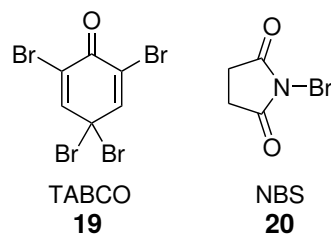
Scheme 2.7 Chemoselective transthioacetalization of **17** [36].

While the condensation reaction between carbonyl compounds and thiols have been known for long time to be catalyzed by dry HCl gas [37], Lewis acid catalyst such as $\text{BF}_3 \cdot \text{OEt}_2$ [38], ZnCl_2 [39] and AlCl_3 [40] are more commonly used. More recently, milder and more environmentally friendly catalysts have been reported.

Firouzabadi *et al.* [36] reported that 10 mol % of I_2 catalyzes the condensation reaction under mild conditions in excellent yields. Aliphatic and aromatic aldehydes condensed with propane-1,3-dithiol at room temperature to afford dithianes in 90% or better yields. The reaction took typically 10 minutes or less to complete. Ketones were also reported to be protected as their *S,S*-acetals in good to excellent yields under the same conditions. However, the reaction proceeded significantly slower with ketones than with aldehydes, which allows to selectively protect aldehydes in the presence of ketones. The catalyst was also reported to transthioacetalize *O,O*-acetals, *O,O*-ketals, *O,S*-acetals and acylals ($\text{R}-\text{C}(\text{OAc})_2$) into their corresponding *S,S*-acetals and -ketals in good to excellent yields. In addition, Samajdar *et al.* [41] reported similar near quantitative yields when 10 mol % of iodine was used as a catalyst to thioacetalize propanal and benzaldehyde with ethanethiol in THF at room temperature. In those cases reaction took 30 minutes to complete.

A year later, 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TABCO) **19**, *N*-bromosuccinimide (NBS) **20** (Scheme 2.8) and Br_2 were reported by Iranpoor *et al.* [42] to catalyze thioacetalization and transthioacetalization under similar mild conditions as I_2 . The catalysts afforded cyclic dithianes from wide range of aldehydes, ketones, *O,O*-acetals and acylals in more than 80% yields, and typically over 90% isolated yields were reported. Interestingly, Iranpoor *et al.* also reported that the catalysts would transform aldehydes and ketones to acyclic

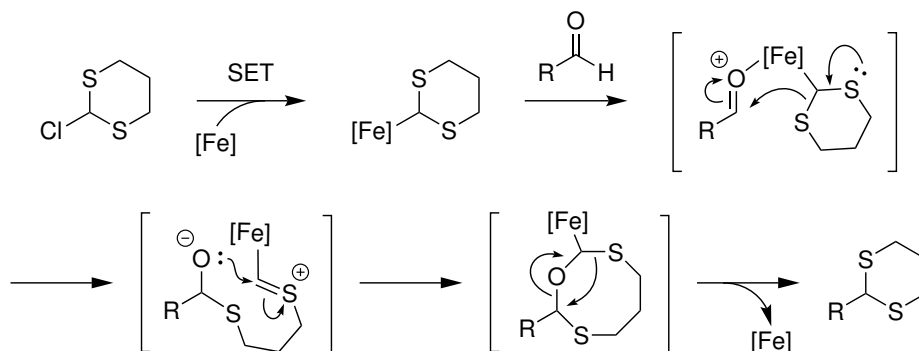
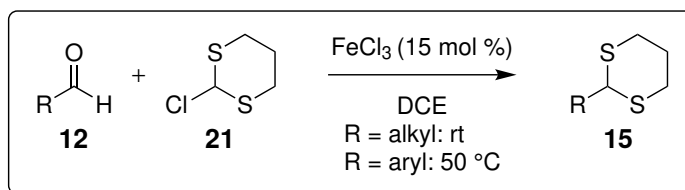
dithioacetals in 90–97% yields when benzylthiol, 1-butylthiol and ethylthiol were used as nucleophiles in the condensation. While the catalysts performed practically similarly, the authors conclude that using NBS and TABCO is advantageous due to difficulties and safety concerns arising from handling liquid bromine.



Scheme 2.8 Structures of 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TABCO) and N-bromosuccinimide (NBS).

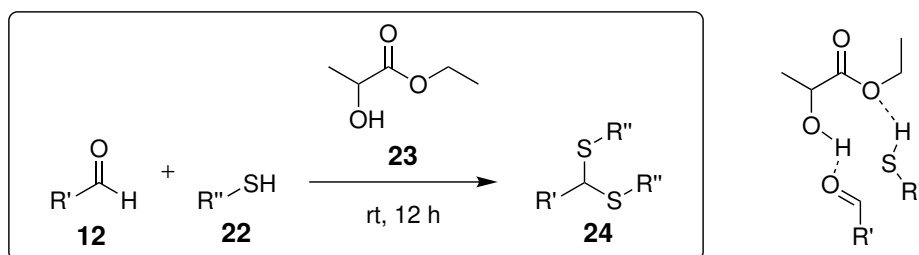
Iranpoor *et al.* [42] also concluded that while TABCO, NBS and Br₂ were observed to catalyze the reaction, the mechanism of the catalysis was not clear. They nevertheless suggested that the catalysis could be caused by the presence of electrophilic bromine, but they also made a remark that the catalysis by *in situ* generated HBr cannot be ruled out. In the same year, Kamal and Chouchan [35] also reported that NBS catalyzes thioacetalization to yield cyclic dithianes from aromatic aldehydes under very similar conditions that Iranpoor *et al.* used in their study. Contrary to the mechanistic suggestion by Iranpoor *et al.*, Kamal and Chouhan explained that the reaction might be catalyzed by HBr which is generated by initial reaction of NBS and dithiol. However, they also noted that the possibility of NBS generating catalytic Br₂ *in situ* cannot be ruled out.

A versatile, mild and odorless thioacetalization process utilizing simple iron catalyst, 15 mol % of FeCl₃, was reported by Lai *et al.* [43]. Instead of propane-1,3-dithiol **13** they used solid 2-chloro-1,3-dithiane **21** to form dithianes from aromatic and aliphatic aldehydes (Scheme 2.9). An array of aromatic aldehydes containing both electron withdrawing and donating groups were used successfully in the reaction to afford dithianes in good yields; with a couple exceptions, over 80 % yields were acquired. Secondary and tertiary aliphatic aldehydes were transformed into their corresponding dithioacetals in 80 % yields. Primary aldehydes, propionaldehyde and butyraldehyde, only afforded dithianes in 58 % and 54 % yields respectively. The most prominent disadvantage of the reported method compared to conventional methods, *i.e.*, using propane-1,3-dithiol and an acid catalyst, seems to be significantly longer reaction time. Reaction time for electron rich aromatic aldehydes was reported to be 4–12 h and in the case of electron poor aldehydes the reaction took 12–24 h.



Scheme 2.9 FeCl_3 catalyzed thioacetalization of aldehydes and proposed mechanism. [43]

Ethyl lactate **23**, a nontoxic bio-based solvent, was reported by Wan *et al.* [44] to mediate thioacetalization under mild and catalyst-free conditions. According to the authors, their method eliminates the need for toxic catalysts and volatile organic solvents while enabling more green and biodegradable ethyl lactate to be used as both solvent and reaction activator. Thioacetalization of benzaldehyde and various aryl aldehydes with ethanethiol, benzenethiol and butane-1-thiol at room temperature produced dithioacetals in reasonable 69–84% yields after 12 h. No improvement in yield was observed when the reaction of *para*-chlorobenzaldehyde and ethylthiol was conducted in temperatures ranging from room temperature to 80 °C. In addition, cyclic 1,3-dithiolanes were produced in 62–72% yields from aromatic aldehydes. Wan *et al.* suggested that ethyl lactate may mediate the reaction by activating both thiol and aldehyde as outlined in Scheme 2.10.



Scheme 2.10 Ethyl lactate **23** mediated thioacetalization of aldehydes and proposed model of activation of aldehyde and thiol. [44]

The idea of catalyst free thioacetalization by Wan *et al.* [44] was not novel. Perin *et al.* [45] used glycerol, a byproduct of biodiesel production, as a solvent to induce thioacetalization under catalyst-free conditions. They reacted various aldehydes and ketones, both aromatic and aliphatic, with benzenethiol which produced corresponding dithioacetals and -ketals in good to excellent yields, *e.g.*, benzaldehyde afforded **9** in 96% isolated yield. In addition,

they used ethane-1,2-dithiol to produce cyclic dithiolanes from aldehydes and ketones. The greatest disadvantage of the method used by Perin *et al.* compared to the method by Wan *et al.* is that glycerol was heated to 90 °C for 2 to 18 hours to obtain the *S,S*-acetal products, which means that the reaction conditions are harsher and more energy consuming than in the case of ethyl lactate.

Akhlaghinia and Makarem [46] demonstrated that various ketones and aldehydes are protected as dithianes under catalyst free conditions in refluxing nitromethane. Aromatic and aliphatic aldehydes were reported to react cleanly with dithiol **13** to yield dithianes in 88 % yields or better after 5–50 minutes. While nitromethane enables reactions complete faster than ethyl lactate or glycerol, the method suffers from harsh conditions as nitromethane boils at 101.20 °C; in addition, the use of petroleum derived nitromethane instead of bio-based solvents can be considered as a disadvantage [47].

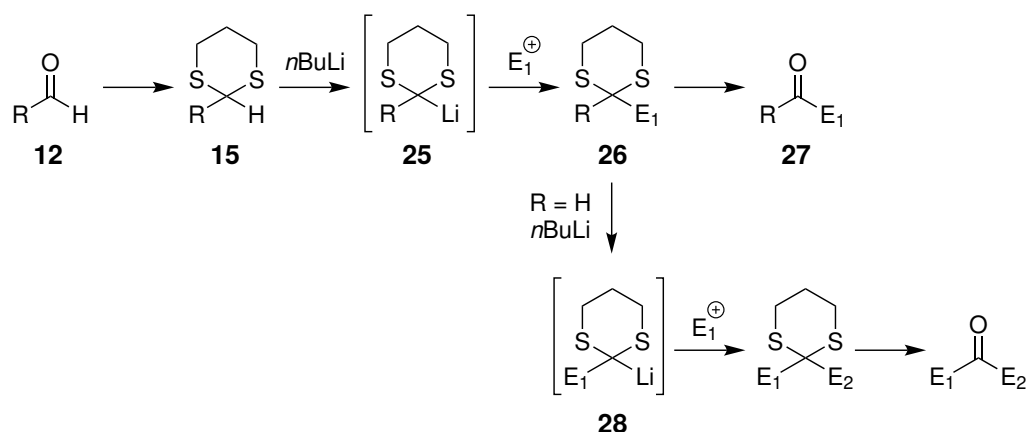
2.3 Corey–Seebach Reaction

In synthesis of complex molecules, it is advantageous to recognize structural subunits in the target structure, which can be assembled into the target structure by known synthetic operations. These subunits can be in turn considered to be made from their subunits by known or conceivable synthetic operations. These subunits are called synthons, a term originally introduced by E.J. Corey in 1967. [48]

Frequently, the reactions in organic chemistry are polar in nature, in which a nucleophilic site in a molecule reacts with an electrophilic site in the same or other molecule to form a bond. Nucleophilic sites can be called donors (d) and electrophilic sites acceptors (a). In molecules containing heteroatoms donor and acceptor sites form an alternating reactivity pattern in the carbon skeleton. In organic synthesis, this pattern often poses a limitation how different molecules can react. For example, 1,2-disubstituted products are more difficult to synthesize than 1,3-disubstituted products from two heteroatom containing synthons, because this would involve coupling two sites with similar polarity. The same limitation applies to any product with 1,2n-disubstitution pattern. [49]

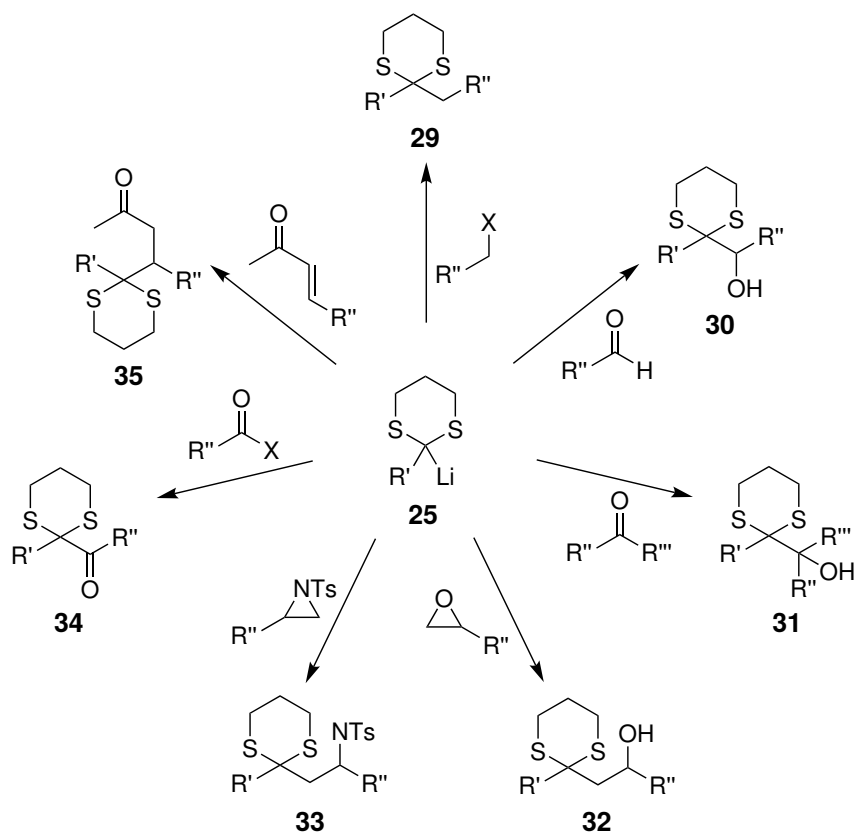
To overcome the difficulty of coupling two sites with similar polarity, a synthetically equivalent reagent with reversed polarity can be utilized. This polarity reversed reagent is said to have reactivity umpolung. For example, normal reactivity of carbonyl carbon is electrophilic, but a reactivity umpolung of carbonyl would be a reagent in which carbonyl carbon acts as a nucleophile. The polarity change can be achieved by multiple different strategies, but for the purpose of synthesizing complex molecules, one of the most useful strategies is to temporarily change the polarity of functional group. [48, 49]

In 1965 Corey and Seebach published an efficient method to temporarily reverse the normal reactivity of carbonyl compounds, namely aldehydes. At first carbonyl **12** is protected as dithiane **15**, as described in section 2.2. The proton on original aldehyde carbonyl carbon becomes acidic as described in section 2.1. The acidic proton can then be deprotonated with strong base such as *n*-butyllithium to yield a lithium carbanion **25** which is a strong nucleophile. This nucleophile can then react with a wide variety of electrophiles to yield dithiane **26**, which can be then hydrolyzed back to carbonyl **27**. Additionally, if unsubstituted 1,3-dithiane **6** is used, a second deprotonation yields again a nucleophilic dithiane **28**. This strategy can be used to induce a second nucleophilic attack. [5, 6, 50] The overall reaction is shown in Scheme 2.11.



Scheme 2.11 . Adapted from [7].

Lithiated 1,3-dithianes **25** undergo alkylation with a wide variety of alkyl halides to yield alkylated *S,S*-acetals **29** (Scheme 2.12). The reaction proceeds particularly fast with primary alkyl iodides and benzylic halides. Secondary iodides and primary and secondary bromides can be also used, but in these cases longer reaction times should be expected. In case of alkyl chlorides, the reaction is generally feasible only when allylic and benzylic chlorides are used. The alkylation reaction fails with some alkyl halides due to competing elimination, *e.g.*, in case of cyclohexyl iodide. In other cases, carrying out the alkylation at low temperatures suppresses the elimination. Additionally, tertiary alkyl halides cannot be used in the alkylation. [5, 7, 50]



Scheme 2.12 Reactions of lithiated 1,3-dithiane with various electrophiles. Adapted from [8].

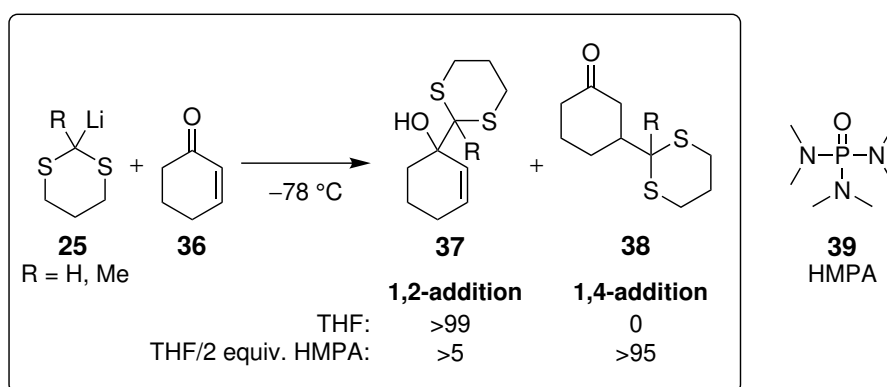
Aldehydes and ketones react readily with lithiated 1,3-dithianes **25** affording α -hydroxy dithianes **30** and **31**. To minimize enolization, aldehydes and ketones should be added to solution of carbanion **25** at $-78\text{ }^{\circ}\text{C}$. Dehydration of the α -hydroxy dithianes by strong acid affords ketene thioacetals if R' in **30** or **31** is proton. If imine is used instead of carbonyl compound, α -amino dithianes are formed. [5, 50]

The reaction of lithiated 1,3-dithianes **25** with epoxides yields β -hydroxydithianes **32** by epoxide ring opening at the less hindered carbon [5, 50]. This is especially useful and a widely used reaction in natural product synthesis as enantiomerically pure epoxides are readily available. The use of chiral epoxides enables the synthesis of dithiane protected, enantiopure β -hydroxycarbonyls in a single step reaction [7]. Deprotection of β -hydroxydithiane produces 1,3-substitution pattern which can be also achieved by the classical aldol reaction without changing carbonyl polarity. However, the umpolung strategy has several advantages over the aldol reaction. Besides having the carbonyl group protected and being able to choose the configuration of α -hydroxy group before the carbon–carbon bond forming reaction, the reaction is not reversible like aldol reactions. In addition, carbonyl self–condensation does not compete when the umpolung strategy is used. [51] Similarly to epoxides, Osborn *et al.* [52] reported that enantiopure N -tosyl aziridines reacted with lithiated 1,3-dithianes **25** to produce ring opened products, β -tosylaminodithianes **33**.

Acylation of lithiated 1,3-dithianes **25** leads to protected 1,2-carbonyl compounds **34**. The difficulty of acylating lithiated 1,3-dithianes is to obtain only monoaddition products when those are desired. Consequently, the success of the reaction depends on the relative reactivities of the carboxylic acid derivative and the generated ketone towards nucleophilic attack by **25**. To avoid the formation of a diadduct product, lithiated 1,3-dithiane **25** should be added to a large excess of acylating agent, typically acid chloride or ester. Acylation can be also conducted with nonenolizable acylating derivatives such as dimethylformamide, aromatic nitriles and carbon dioxide. In these cases carbonyl compounds are obtained only after workup and diaddition is not possible. When dimethylformamide is used, **34 R'' = H** is obtained, in case of carbon dioxide, product is **34 R'' = OH**, and using aromatic nitriles yields **34 R'' = Ar** after workup. [6, 50]

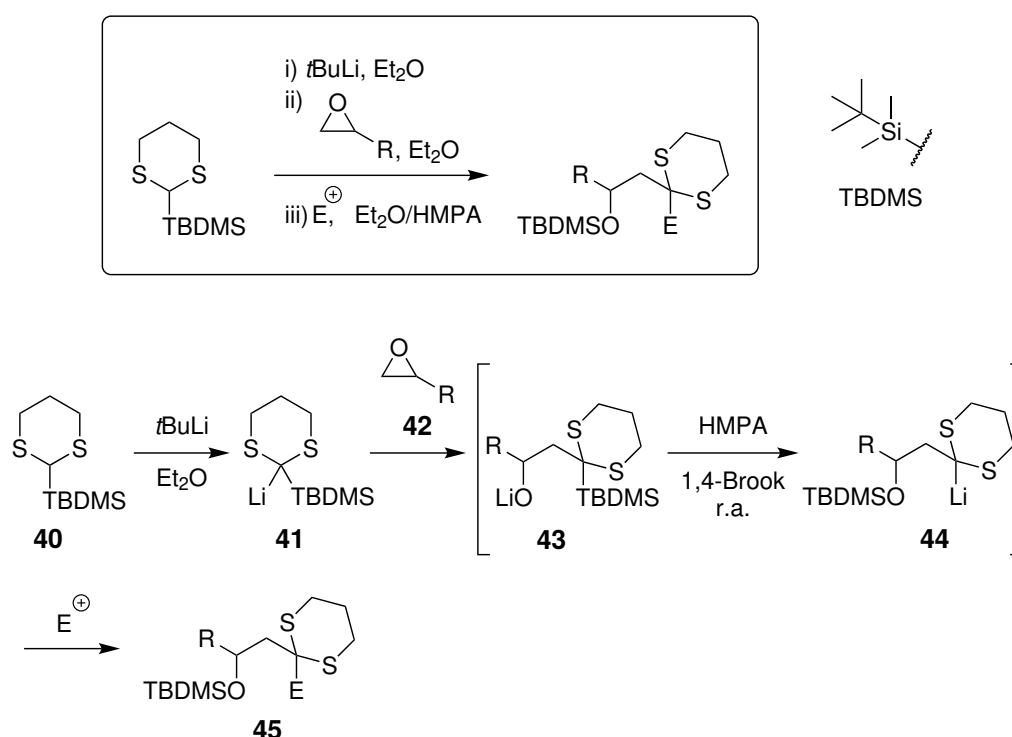
If α,β -unsaturated carbonyl compounds are used as electrophiles, lithiated 1,3-dithianes **25** react preferentially by 1,2-addition to produce compounds like **30** and **31**. One way to form compounds with masked 1,4-dicarbonyl relation, such as **35**, is to use alkylation instead of conjugate addition. For example, alkylating **25** with $(\text{EtO})_2\text{CH}(\text{CH}_2)_2\text{Br}$ will yield the desired 1,4-dicarbonyl relation. Similarly, using $(\text{EtO})_2\text{CHCH}_2\text{Br}$ would lead to 1,3-dicarbonyl relation. [5, 6]

Sikorski and Reich [53] reported that the lithiated 1,3-dithiane in THF exists as a contact ion pair (CIP), in which there is a carbon–lithium bond. In the case of CIP, only 1,2-addition to cyclohexanone **36** was observed, yielding **37** (Scheme 2.13). However, they showed that the addition of hexamethylenephosphoramide (HMPA) **39**, a highly polar aprotic solvent, caused the lithiated 1,3-dithiane to form separated ion pairs (SIP) in solution. In SIP, carbanion and lithium counter ion are separated by at least one layer of solvent molecules. Upon addition of HMPA, regioselectivity of the reaction changed to favor kinetic 1,4-addition, yielding almost exclusively **38**. They suggested that CIP to SIP transition caused by addition of HMPA was an important factor in the change of regioselectivity. In addition, Sikorski and Reich proposed that HMPA affected reaction regioselectivity by decreasing the Lewis acidity and catalytic effect of the lithium cation.



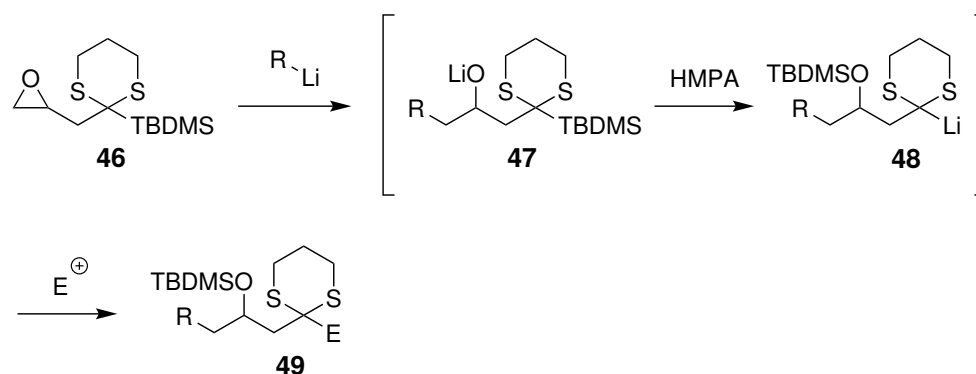
Scheme 2.13 Addition of 2 equivalents of HMPA **39** changes the regioselectivity of the reaction from 1,2-addition to 1,4-addition. Adapted from [53].

2-silyl substituted 1,3-dithianes can be utilized in a multicomponent coupling reactions. Smith and Boldi [54] reported that dithiane **40** can be coupled with two different electrophiles in one-pot reaction (Scheme 2.14). In the reaction, **40** was lithiated with tert-butyllithium to produce lithiated dithiane **41**, which was then reacted with an epoxide **42** to afford the intermediate lithium oxyanion **43**. When the oxyanion intermediate is treated with HMPA, it undergoes 1,4-Brook rearrangement. In the Brook rearrangement silyl group migrates from carbon to oxyanion, which simultaneously protects the oxyanion as silyl ether and generates a new dithiane carbanion **44**. The carbanion **44** can then be used to attack a second electrophile affording a three-component product **45**.

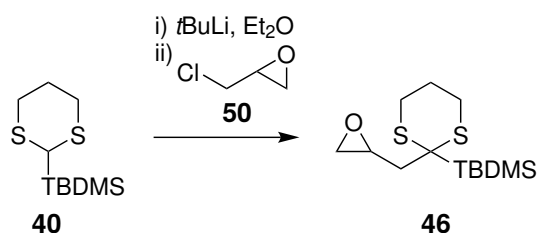


Scheme 2.14 Multicomponent coupling of 2-silyl-1,3-dithianes [54].

Later Smith and Xian [55] took the idea of multicomponent reaction involving 1,3-dithiane as anion stabilizing groups even further. They reported that similar oxyanion than **43** can be also generated by nucleophilic attack to epoxide **46**. They used different lithiated 1,3-dithianes as nucleophiles to produce the oxyanion intermediate **47**, which was then transformed to lithiated 1,3-dithiane **48** by 1,4-Brook rearrangement. After the rearrangement, carbanion is able to react with electrophile to yield the final multicomponent product **49**. Epoxide **46** can be easily prepared by deprotonating **40** and then adding epichlorohydrin **50** (Scheme 2.16).



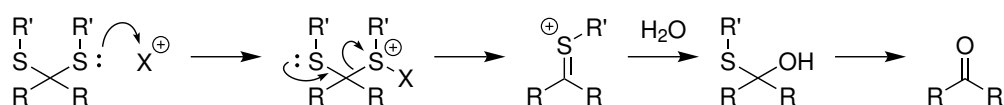
Scheme 2.15 Multicomponent coupling of **46** [55].



Scheme 2.16 Synthesis of **46** [55].

2.4 Deprotection of *S,S*-acetals

There exist multiple ways in literature to deprotect 1,3-dithianes and dithioacetals [31]. Deprotection methods can be divided into three common classes: metal coordination, oxidation and alkylation. In the majority of methods, the cleavage of *S,S*-acetals is initiated by activation of sulfur to transform it into a good leaving group. The activation is then followed by hydrolysis to produce the desired unprotected carbonyl compound. [20, 56] General mechanism for the hydrolysis is presented in Scheme 2.17.



Scheme 2.17 Deprotection of *S,S*-acetals involves activation of sulfur and subsequent hydrolysis to carbonyl. [20]

Despite of the large number of published methods, there is a lack of methods which would be mild, versatile, safe and inexpensive. Many of the methods typically suffer from poor selectivity, long reaction times and harsh conditions which lead to poor yields and formation of byproducts. [56] This has often led to problems when dithiane-based umpolung strategies has been used, especially for very complex and sensitive molecules. As there is no single method that can be generally applied, deprotection of 1,3-dithianes requires careful consideration based on the structure of substrate. [7, 57] In some complex cases, only meticulous screening of different methods has provided desirable results [58, 59].

Historically one of the most common ways to deprotect *S,S*-acetals is the hydrolysis in the presence of mercury(II) salt such as HgCl_2 , $\text{Hg}(\text{ClO}_4)_2$ and HgO [31, 56, 60]. This method is still commonly used in organic laboratories despite the known toxicity and potential environmental hazards involved in handling mercury salts [56, 61]. Other common metal salts that can be used in deprotection are silver(I) salts such as AgNO_3 and AgClO_4 , which are less harmful than mercury salts, but are also more expensive [31, 56].

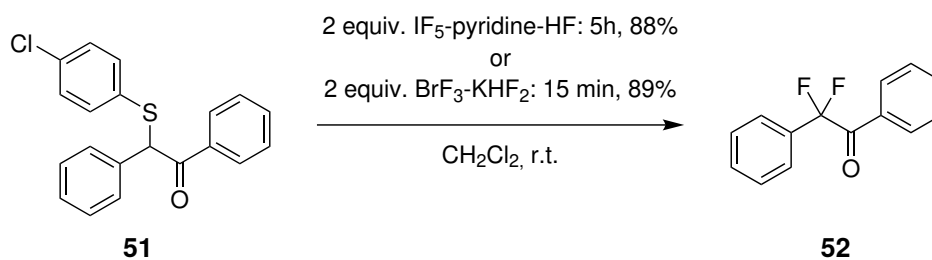
Oxidative strategies of cleaving *S,S*-acetals typically involve initial oxidation of sulfur in *S,S*-acetal into sulfoxide, which are more labile and better leaving groups than thiolates [56]. One of the most common oxidizing agents used in the deprotection is NBS **20**, which was initially studied by Corey and Erickson [60] as an alternative to mercury(II) reagents. According to the authors NBS enabled facile hydrolysis of 2-acyl-1,3-dithianes where as mercuric reagents performed poorly with these type of compounds.

Finally, alkylation can cleave *S,S*-acetals by converting sulfides into sulfonium salts, which are better leaving groups than thiolates. Iodomethane is a common methylating agent used in the alkylation. [31, 56]

2.5 Transformations of Sulfur Groups

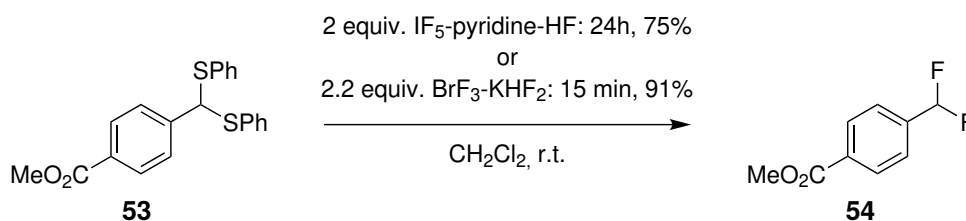
S,S-acetals can be also reduced to methylene by hydrogenolytic desulfurization. The reaction is typically done with Raney nickel without any external hydrogen source as Raney nickel itself provides enough hydrogen for the reduction. Besides *S,S*-acetals, Raney nickel desulfurizes a wide variety of sulfur containing groups, including thiols, disulfides, sulfoxides and sulfones, which should be taken into account if only *S,S*-acetal reduction is desired. [33, 62] In addition to Raney nickel, other nickel containing heterogeneous reagents can be used. For example, Nickel containing complex reducing agents (NiCRA) are easily prepared and nonpyrophoric reducing agents, which are capable both completely and half desulfurizing *S,S*-acetals. In the latter case less reactive NiCRA was used to convert *S,S*-acetal to sulfide. [63]

Sulfides such as *S,S*-acetals and orthothioesters can be used to introduce fluorine atoms into molecules. Hara *et al.* [64] reported that IF_5 -pyridine-HF can be used in desulfurizing fluorination reactions. According to the authors IF_5 -pyridine-HF is a safe and easy to handle fluorinating reagent as it is an air- and moisture-stable solid. Desulfuration-fluorination reaction of α -arythio ketone **51** with IF_5 -pyridine-HF gave the difluorinated compound **52** in 88% yield after 5 hours at room temperature (Scheme 2.18). Later Shishimi and Hara [65] reported that another air-stable, but more reactive fluorinating reagent, BrF_3 - KHF_2 , can be used to achieve the same reaction with 89% yield in 15 minutes at room temperature.



Scheme 2.18 Desulfuration-fluorination of α -arylthio ketone **51**. [64, 65]

Hara *et al.* [64] reported that IF_5 -pyridine-HF can be used to transform dithioacetals of aldehydes and ketones to gem-difluoro compounds. The same reaction was also done with BrF_3 - KHF_2 by Shishimi and Hara [65]. As with the difluorination reaction of compound **51**, BrF_3 - KHF_2 was faster and produced generally better yields than IF_5 -pyridine-HF. For example, with IF_5 -pyridine-HF dithioacetal **53** afforded the difluorinated product **54** in 75% yield after 24 hours, whereas with BrF_3 - KHF_2 the same reaction took 15 minutes and the yield was 91% (Scheme 2.19).



Scheme 2.19 Desulfuration-fluorination of dithioacetal **53**. [64, 65]

Analogously to dithioacetals, aryl orthothioesters are transferred to trifluoromethyl group with BrF_3 - KHF_2 . However, the fluorinating agent brominated the aromatic ring simultaneously. [65] Matthews *et al.* [66] prepared aromatic trifluoromethyl compounds **57** from orthothioesters **55** with two step reaction: first aromatic orthothioester was treated with 1,3-dibromo-5,5-dimethylhydantoin (DBH) **56** or NBS **20**, followed by addition of HF-pyridine complex (Scheme 2.20). Aromatic trifluoromethyl compounds were obtained in 34–59% isolated yields. If aromatic ring had electron donating substituent, bromination of the ring was observed.

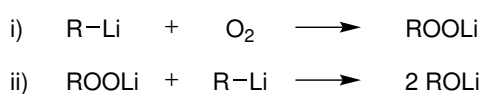
3. CARBON OXIDATION OF DITHIOACETALS AND 1,3-DITHIANES

Reactions involving lithiated organic compounds such as 2-lithio-1,3-dithianes discussed in chapter 2 have to be conducted strictly under inert atmosphere. Besides the possibility of moisture in air protonating strongly basic reactants, all organoalkali metal compounds are strongly reactive towards oxygen in air. [14, 15]

The first section of this chapter explains the basic theory and mechanisms behind the aerobic oxidations of organolithium compounds. In the second section aerobic carbon oxidation is considered in terms of 2-lithio-1,3-dithianes and the third section discusses about how the oxidation of lithiated 1,3-dithianes is related to this study.

3.1 Oxidation of Organolithium Compounds

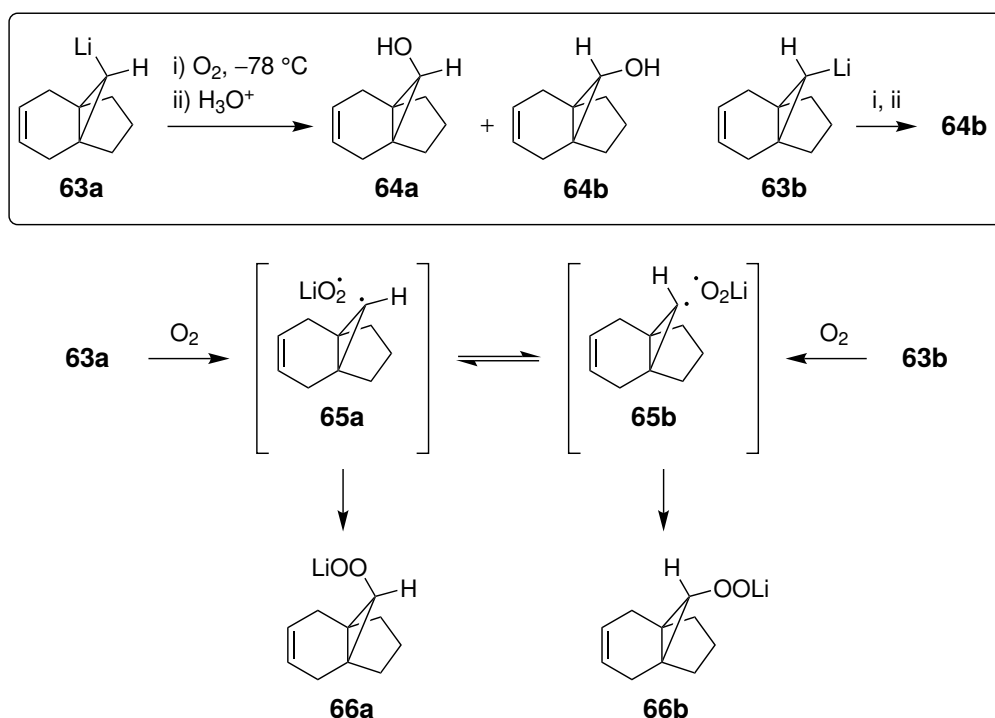
Alkylolithium compounds are thought to react with dioxygen O₂ in a two step oxidation reaction (Scheme 3.1). In the first step alkylolithium (RLi) reacts with O₂ to form a lithium peroxide (ROOLi), which then reacts rapidly with organolithium compounds to give two equivalents of lithium alkoxide (ROLi). The lithium alkoxide yields alcohol upon hydrolysis. [14, 15]



Scheme 3.1 Alkylolithiums react with O₂ in a two step reaction to produce lithium alkoxides [14, 15].

The first step of oxidation to form the lithium peroxide intermediate likely involves a radical process. Warner and Lu [71] studied oxidation of lithiated propellanes **63a** and **63b** (Scheme 3.2). When O₂ was bubbled through solution of **63b**, only isomer **64b** was obtained after aqueous workup. Similar oxygenation of **63a** resulted in 2.8:1 mixture of isomers **64a** and **64b**. Warner and Lu suggested that initial formation of radical pair **65a** and **65b** leads to epimerization of the product. Recombination of radical pair leads to corresponding lithium peroxide intermediates **66a** and **66b**. However, Warner and Lu noted that they could not explain if the preferred formation of **64b** was due to greater stability of **65b** or faster recombination of **65b** than **65a**. More recently, Möller *et al.* [72]

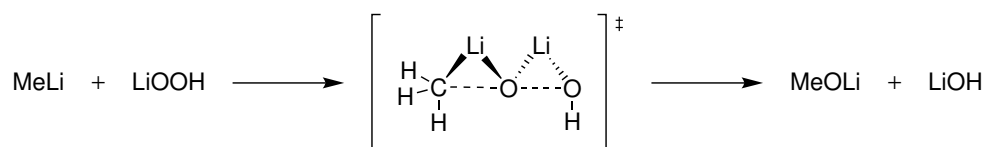
observed similar loss of stereochemistry in oxidations of configurationally stable *cis*- and *trans*-cyclopropyl lithium compounds with O_2 . They concluded that this is due to radical intermediates forming in the oxidation.



Scheme 3.2 The formation of radical intermediate **65** leads to epimerization of the product **66**. [71]

Lithium peroxides such as **66** are oxenoids. Oxenoids are compounds in which oxygen is bonded to metal atom (M) and to a leaving group (LG), thus having general structure of $LG-O-M$. In lithium peroxides the leaving group is RO^- and metal is lithium cation. Oxenoids are capable of transferring electrophilic oxygen atom to a nucleophile such as organolithium compound. [73–75] First report of this type of oxidation of organolithium compounds with lithium peroxides was by Müller and Töpel [76] in 1932 when they obtained phenol and tetralol from a reaction of lithiated tetralin hydroperoxide and phenyllithium.

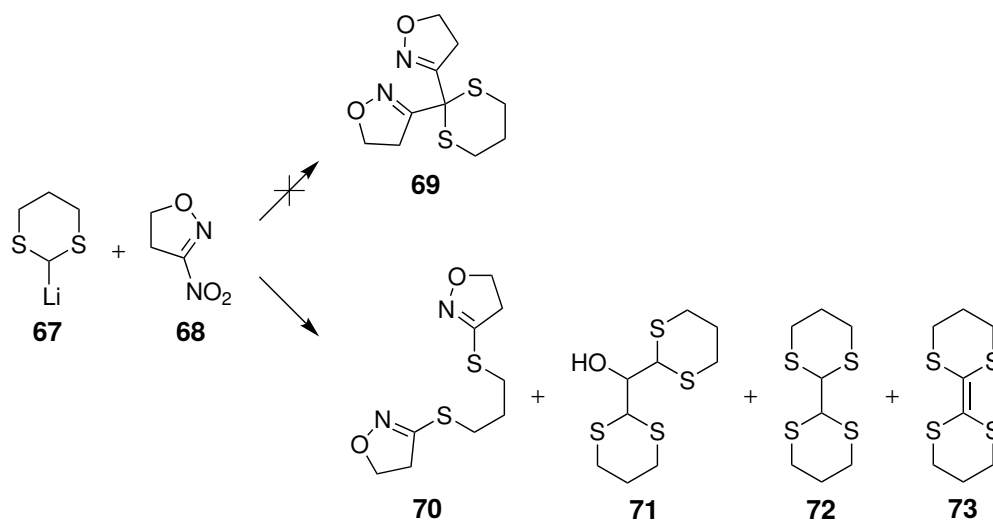
In the second step of Scheme 3.1, alkyllithium compounds are quickly reacting with lithium peroxide compounds to form two equivalents of lithium alkoxides. Unlike the oxidation with O_2 , experimental evidence indicates that the second reaction happens with retention of configuration at alkyllithium carbon. This suggests that the second reaction likely proceeds via S_N2 type of mechanism rather than via electron transfer and subsequent recombination. [71, 72, 77]. Boche *et al.* [78] conducted model calculations of the reaction of MeLi with LiOOH at MP2(fc)/6-31G(d) level. They reported that the reaction has a S_N2 type transition state leading to products MeOLi and LiOH (Scheme 3.3).



Scheme 3.3 The calculated S_N2 type transition state leading to the lithium alkoxide [78].

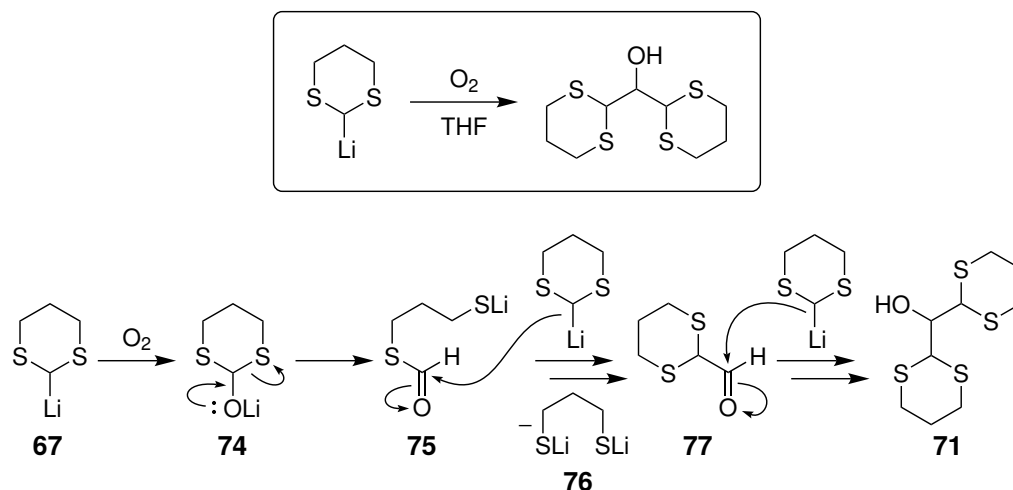
3.2 Lithium Alkoxides Derived from 1,3-Dithianes

Wade *et al.* [16] reported that the reaction of 2-lithio-1,3-dithiane **67** and 4,5-dihydro-3-nitroisoxazole **68** did not produce the expected displacement product **69**, but instead a mixture of unexpected displacement product **70**, alcohol **71**, a dimer of dithiane **72** and traces of alkene **73** was observed (Scheme 3.4). Further investigation of the reaction linked the formation of **70** and **71** to auto-oxidation of **67**. Wade *et al.* suggested that in the reactions where **68** was present, oxygen source could be either insufficiently degassed solvent or, in the cases where care was taken to exclude air from reaction, **68** itself.



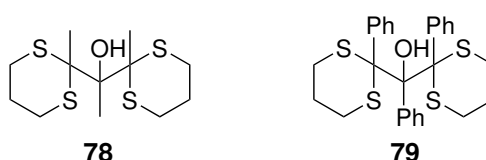
Scheme 3.4 The reaction of 2-lithio-1,3-dithiane **67** with 4,5-dihydro-3-nitroisoxazole led to unexpected products **68** [16].

When Wade *et al.* [16] conducted aerobic oxidation of **67** in the absence of electrophile **68** only formation of alcohol **71** was observed (Scheme 3.5). They explained the formation of **71** by initial reaction of **67** with oxygen. The oxidation was assumed to first form lithium peroxide anion and subsequently lithium alkoxide **74**. Wade *et al.* hypothesized that ring opening of **74** would lead to formation of thioester intermediate **75** which would then react with unoxidized **67** via addition-elimination mechanism to form dilithium 1,3-propanedithiolate **76** and aldehyde **77**. Nucleophilic attack of excess unoxidized **67** to **77** would finally lead to the alcohol product **71**. When electrophile **68** was present in the reaction, nucleophilic attack of **76** to **68** would then explain the formation of **70**.



Scheme 3.5 Aerobic oxidation of **67** in the absence of electrophile [16].

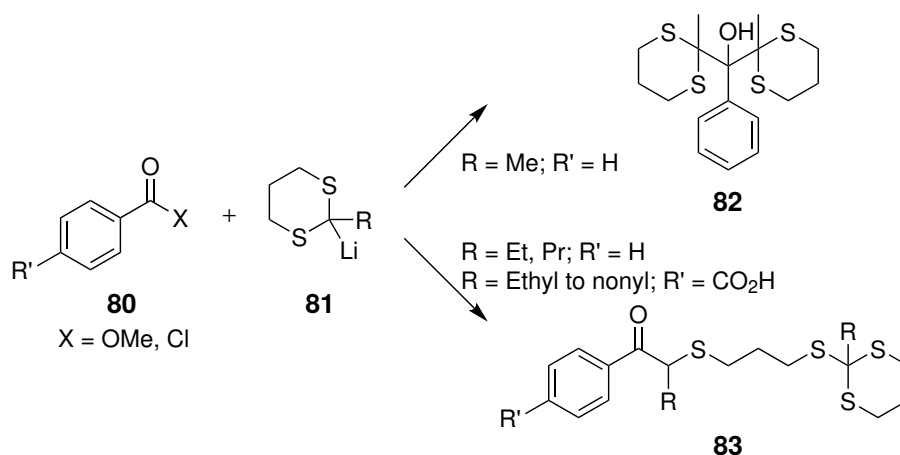
The formation of **71** has been proposed to form in reaction of **67** and THF [79]. This seems unlikely as no other reports of similar reactions could be found in literature despite the common usage of THF as a solvent for lithiated dithianes; in addition, no justification for the reaction was given in the article. Argade *et al.* [17] observed formation of **71** when one year old *n*-butyllithium was used to lithiate 1,3-dithiane. Oxidizing impurity in old *n*-butyllithium (possibly *n*-BuOOLi) was suggested to be the cause for the reaction. Furthermore, Argade *et al.* observed that when the old *n*-butyllithium was used to lithiate 2-methyl-1,3-dithiane and 2-phenyl-1,3-dithiane similar alcohol products to **71** were produced, but having either methyl (**78**) or phenyl (**79**) substituents (Scheme 3.6). This confirmed that the carbon next to hydroxyl originates from 1,3-dithiane.



Scheme 3.6 Oxidation products reported by Argade *et al.* [17].

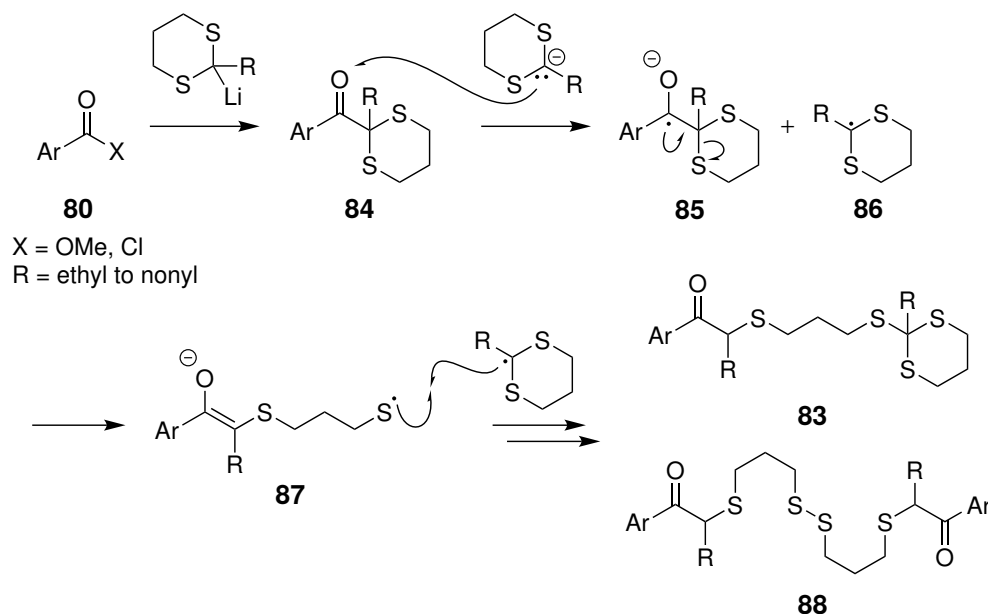
3.3 Background and Motivation for the Study

Valiulin *et al.* [18] tried to produce similar α,α -bis(dithianyl) alcohols than **71**, **78** and **79** by double nucleophilic addition of lithiated alkyl dithianes **81** to acyl chlorides and esters (**80**). They observed that the reaction only gave the expected bisaddition product **82** when 2-methyl-1,3-dithiane was used as a nucleophile. If the substituent in dithiane was larger than methyl unexpected ring opening occurred after the first addition which then led to formation of orthothioester **83**.



Scheme 3.7 Products obtained by Valiulin *et al.* [18].

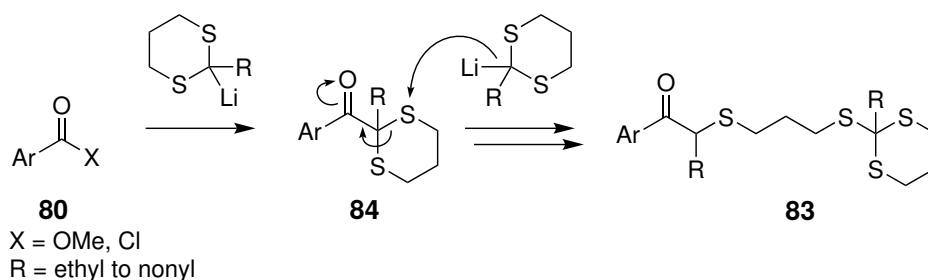
According to Valiulin *et al.* [18] the most likely mechanism involves initial formation of ketone **84** after the first addition of lithiated alkyl dithiane **81** to carboxylic acid derivative **80**. Instead of second addition to this ketone to form tertiary alcohol, a single-electron transfer from **81** to **84** takes place to yield ketyl radical **85** and dithiane radical **86**. The former then undergoes mesolytic cleavage to produce ring-opened enolate **87**. The enolate then recombines with dithiane radical **86** to form an enolate of **83**, which gives the observed product after aqueous workup. Valiulin *et al.* also observed the formation of dimeric product **88**, which would result from recombination of two **87** radicals.



Scheme 3.8 The single-electron transfer mechanism suggested by Valiulin *et al.* [18].

However, Valiulin *et al.* [18] also pointed out that polar mechanism can not be completely ruled out. In the polar mechanism ring cleavage would result from nucleophilic attack of **81** to sulfur carbon bond in **84**, which would lead directly to an enolate of the observed ortho-thioester product **83**. This type of nucleophilic attacks where carbon atom of the

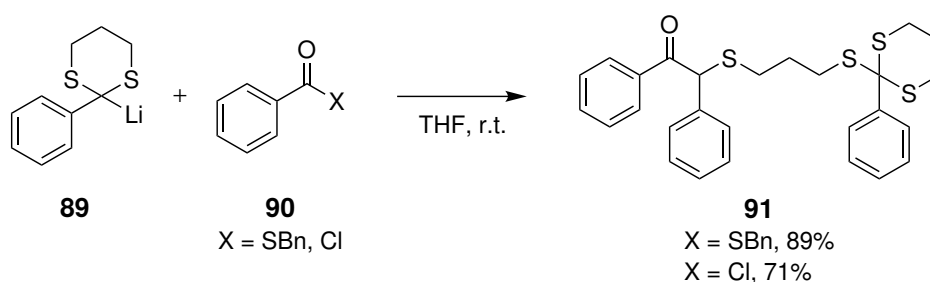
carbon-heteroatom bond acts as a leaving group are well known in organic chemistry [80]. In this case low electronegativity of sulfur and stabilization of carbanion by enolate formation makes nucleophilic attack to sulfur more favorable.



Scheme 3.9 The polar mechanism suggested by Valiulin *et al.* [18].

Considering the reports by Wade *et al.* [16] and Valiulin *et al.* [18], a question arose whether 2-aryl-2-lithio-1,3-dithianes would form a thioester similar to **75** by *in situ* oxidation. Moreover, if the thioester is formed, would it be capable of undergoing a similar attack by unoxidized 2-lithio-1,3-dithiane as carboxylic acid derivative **80** in Scheme 3.9. This would ultimately lead to similar products as described by Valiulin *et al.* in a one-pot reaction.

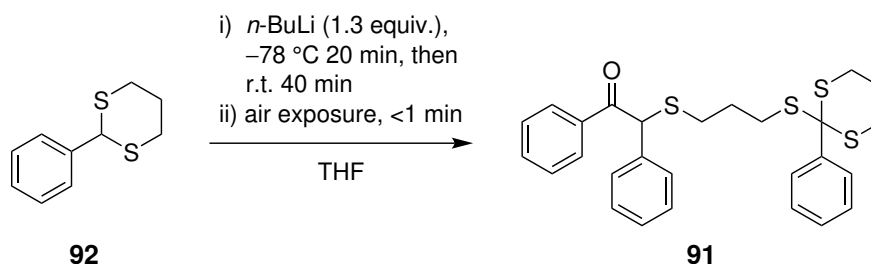
Initial experiment by a colleague [19] showed that reacting 2-phenyl-2-lithio-1,3-dithiane **89** with *S*-benzyl benzothioate **90** afforded orthothioester product **91** similar to orthothioester Valiulin *et al.* reported previously (Scheme 3.10). The yield of the reaction was 89%, which is similar that Valiulin *et al.* obtained from their reactions. This proved that thioester group is able to undergo similar attack as acid chlorides and esters. The same reaction was also tried with benzoylchloride, which produced the same **91** product, albeit with smaller 71% yield.



Scheme 3.10 The reaction of 2-phenyl-2-lithio-1,3-dithiane **89** with a thioester and acid chloride [19].

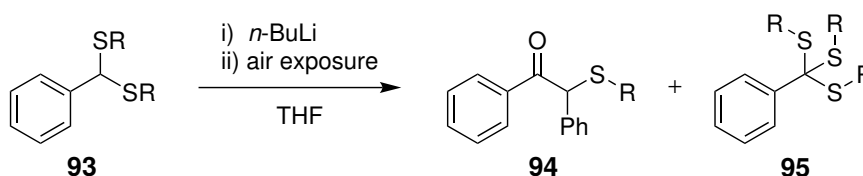
After it was established that preformed thioester worked as hypothesized, Vale *et al.* [19] attempted to oxidize 2-phenyl-2-lithio-1,3-dithiane with O₂ to form the thioester intermediate *in situ*. Simply replacing the argon atmosphere over **89** with oxygen for 5 minutes afforded orthothioester **91** in 69% yield. Using air in the oxidation yielded the orthothioester in 41% and 68% yields after 30 minute and less than minute exposure, respectively. If the

lithiated dithiane was formed at 0 °C minor increase of yield to 71% was observed. After further optimization of reaction conditions, 76% yield of **91** was achieved (Scheme 3.11).



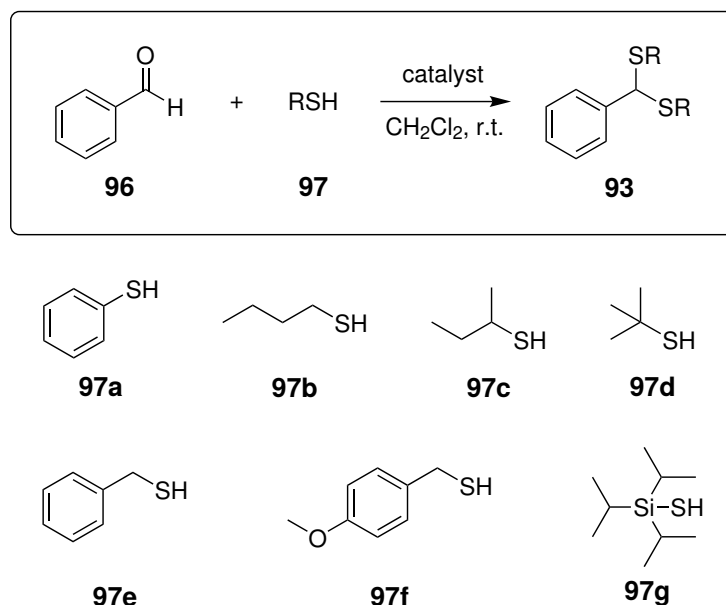
Scheme 3.11 Aerobic oxidation of 2-phenyl-2-lithium-1,3-dithiane [19].

After the optimized procedure for 2-aryl-1,3-dithioacetals oxidation was found, the goal set for this thesis was to evaluate the scope of the oxidation. As only cyclic 1,3-dithianes were used in the initial experiments, it was envisioned that acyclic dithioacetals **93** would afford separate ketone **94** and orthothioester **95** products (Scheme 3.12).



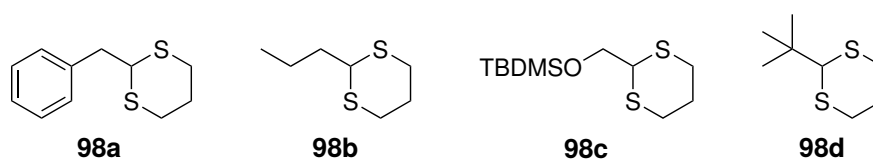
Scheme 3.12 Aerobic oxidation of dithioacetals **93**.

The acyclic dithioacetals **93** to be used in the scope study were planned to be made by thioacetalizing benzaldehyde **96** with a variety of thiols **97** (Scheme 3.13) as this method is the most often used in the literature. Dithioacetals derived from phenyl-, *n*-butyl-, *sec*-butyl and *tert*-butyl thiols (**97a–d**) were anticipated to give information how thiols with different sized substituents affected the oxidation. Dithioacetals derived from benzyl substituted thiols (**97e,f**) were also planned to be made as those would both provide more information about the scope and offer a possibility to cleave the benzyl groups after the oxidation to afford free thiol. Dithioacetal derived from thiosilane **97g** was thought to be an interesting substrate for the oxidation due to the possible [1,4]-S- to O-silyl migration in the lithium enolate intermediate of **94** [81].



Scheme 3.13 Preparation of dithioacetals for the oxidation study.

The second objective of the thesis was to study the scope of the oxidation of 2-alkyl substituted 1,3-dithianes. Four 1,3-dithianes **98a–d** were planned to be prepared for the oxidations by thioacetalizing the corresponding aldehydes with propane-1,3-dithiol. Dithianes **98a–c** were chosen in order to evaluate how the different substituents in the primary alkyl substituted 1,3-dithianes would affect the outcome of the oxidation. The use of secondary alkyl substituted 1,3-dithiane (2-cyclohexyl-1,3-dithiane) in the initial oxidation studies by my colleague was observed to be detrimental for the yield, therefore no further studies with secondary alkyl substituted 1,3-dithianes were planned for the thesis. However, to study the oxidation with tertiary alkyl substituted 1,3-dithiane, **98d** was planned to be made from pivaldehyde.



Scheme 3.14 Preparation of 1,3-dithianes for the oxidation study.

4. RESULTS AND DISCUSSION

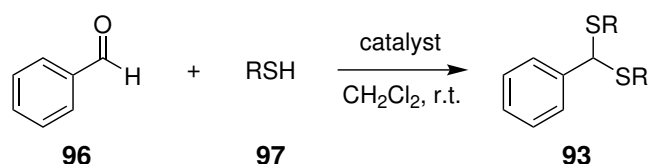
The experimental part of the thesis was done in the synthesis laboratory of the Laboratory of Chemistry and Bioengineering in Tampere University of Technology during June–September 2017. The first section of this chapter discusses about the synthesis of the starting material for the oxidation studies. The second and the third sections introduce the results of the oxidation studies of lithiated dithioacetals and 1,3-dithianes. The synthesis methods and the spectroscopic characterization of the compounds are described in the chapter 6.

4.1 Preparation of Dithioacetals and 1,3-Dithianes

As a part of the thesis, dithioacetals and 1,3-dithianes were prepared for the oxidation studies. This was done by thioacetalizing aldehydes and using the standard procedures found in literature. Mild catalysts such as I_2 and NBS were preferred over more active Lewis acid catalysts due to their easier handling. However, in some cases $BF_3 \cdot OEt_2$ were used if a milder catalyst did not provide satisfactory yields and $BF_3 \cdot OEt_2$ had been reported in literature to successfully catalyze the formation of the desired dithioacetal or 1,3-dithiane. The first two thioacetalizations were done in $CHCl_3$, because the solvent was used in the original literature method [36]. However, because of the toxicity of $CHCl_3$, a less toxic CH_2Cl_2 was used in all the following thioacetalizations without any observable disadvantages.

First dithioacetals **93** were prepared by thioacetalizing benzaldehyde **96** with thiols **97** according to Scheme 4.1. Thioacetalization of benzaldehyde with benzenethiol **97a** yielded the desired dithioacetal **93a** in 66% yield after recrystallization (entry 1, Table 4.1). In this case iodine catalyst provided a sufficient yield of dithioacetal starting material **93a** for the following oxidation study. However, when iodine was used to catalyze the reaction of *tert*-butylthiol and benzaldehyde, no dithioacetal product **93d** was observed by TLC analysis after 70 h reaction (entry 4). With $BF_3 \cdot OEt_2$ the reaction was observed by TLC analysis to produce more byproducts, but nevertheless poor 25% yield of **93d** was still obtained after isolation (entry 5). Iodine was also used in thioacetalization with benzylic thiols **97e** and **97f** (entries 7 and 9). In these reactions iodine also performed poorly, yielding dithioacetals **93e** and **93f** in 47% and 22% yields, respectively.

In an attempt to examine why iodine performed poorly as a catalyst for acyclic dithioacetals, a solid byproduct from reaction of *para*-methoxy benzyl thiol **97f** and benzaldehyde (entry 9) was isolated by column chromatography. ^1H and ^{13}C NMR spectra of the byproduct indicated that the thiol had oxidized to disulfide **99** ($(4\text{-MeO-PhCH}_2\text{S})_2$); the observation was verified by comparing the measured spectra to known literature spectra of the disulfide. Iodine is known to convert thiols into disulfides under a variety of conditions without other reagents [82]. While the disulfide byproduct was easily separated from the desired dithioacetal product by column chromatography, it was observed to readily cocrystallize with dithioacetals **93d,e** which made the purification of solid dithioacetals by recrystallization impractical. In addition, oxidation of thiol competed with the formation of dithioacetal decreasing the yields. A more suitable catalyst than iodine was clearly needed to increase the yields of dithioacetals.



Scheme 4.1 Preparation of dithioacetals **93** by thioacetalization of benzaldehyde **96** with thiol **97**.

Table 4.1 Yields obtained from the preparation of dithioacetals.

Entry ^a	97 Thiol	Catalyst (equiv.) ^b	Reaction time	93 Product	Yield (%) ^c
1 ^d	97a PhSH	I ₂ (0.1)	30 min	93a	66
2	97b <i>n</i> -BuSH	NBS (0.1)	30 min	93b	91
3	97c <i>sec</i> -BuSH	NBS (0.1)	30 min	93c	86
4 ^d	97d <i>tert</i> -BuSH	I ₂ (0.1)	70 h	93d	0
5		BF ₃ · OEt ₂ (0.7)	2 h		25
6		NBS (0.3)	2 h		87
7	97e BnSH	I ₂ (0.1)	35 min	93e	47
8		NBS (0.2)	80 min		96
9	97f <i>p</i> -MeO-BnSH	I ₂ (0.1)	30 min	93f	22
10		NBS (0.2)	70 min		99
11 ^e	97g (<i>i</i> -Pr) ₃ SiSH	NBS (0.2)	117 h	93g	0
12		BF ₃ · OEt ₂ (1.4)	25 h		0 ^f

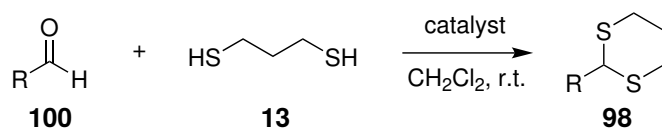
^a Unless otherwise noted, reactions were done in dry CH₂Cl₂ at room temperature. ^b Compared to benzaldehyde ^c Isolated yield. ^d CHCl₃ was used as a solvent without prior drying. ^e Refluxed for 6 h after 23 h. ^f Product was observed on TLC, but it hydrolyzed during aqueous workup

After a literature search, NBS was found to be a promising catalyst for the synthesis of acyclic *S,S*-acetals. NBS proved to be a good choice for a catalyst as tertiary, secondary and primary alkyl thiols afforded dithioacetals in 86–91% yields after isolation. The reactions were complete after 30 minutes in the case of primary or secondary thiols and after 80

minutes in the case of more sterically hindered tertiary thiol (entries 2, 3 and 6, Table 4.1). Benzylic thiols gave close to quantitative yields of dithioacetals when NBS was used as a catalyst (entries 8 and 10).

Thioacetalization reaction of triisopropylsilanethiol **97g** and benzaldehyde was unsuccessful when NBS or $\text{BF}_3 \cdot \text{OEt}_2$ was used as a catalyst (entries 11 and 12, Table 4.1). With NBS only a trace amount of a possible product was observed on TLC, even after attempts to drive the reaction to completion by heating and adding more catalyst. $\text{BF}_3 \cdot \text{OEt}_2$ catalyzed reaction afforded a distinct product spot on TLC. Unfortunately, only a solid which was insoluble in both aqueous and organic solvents was obtained after aqueous workup. No previous reports of dithioacetals derived from thiosilane like **93g** could be found from literature. Alkyl substituted thiosilanes ($\text{R}^1\text{S}-\text{SiR}_3$) and aldehydes (R^2CHO) have been reacted under Lewis acid catalysis to produce dithioacetals $\text{R}^2\text{CH}(\text{SR}^1)_2$ [83]. Analogously, thiol **97g** would produce phenylmethanedithiol $\text{PhCH}(\text{SH})_2$, but it was not observed.

Dithianes **98** were made by thioacetalizing aldehydes **100** with propane-1,3-dithiol **13** (Scheme 4.2). Catalyst was selected case by case based on the yields reported in the literature to same or structurally similar dithianes. Unexpectedly, when iodine was used as a catalyst for thioacetalization of phenylacetaldehyde, only moderate yield of 53% was obtained (entry 1, Table 4.2) in contrast to excellent yield reported in literature for the same thioacetalization reaction [36]. This led to further investigation of the starting material used in the reaction. ^1H NMR spectrum of phenylacetaldehyde used in the reaction indicated that the aldehyde had most likely self condensed under storage. As the aldehyde was used without any prior purification this led to decreased yield. The reaction of butyraldehyde and dithiol **13** gave an excellent yield when catalyzed by $\text{BF}_3 \cdot \text{OEt}_2$ (entry 2). Dithianes **98c** and **98d** were obtained in 33% and 62% yields, respectively (entries 3 and 4). While the latter yield was poor, the reaction provided enough dithiane starting material for the following oxidation studies, so there was no need to optimize the yield any further.



Scheme 4.2 Preparation of dithianes **98** by thioacetalization of aldehydes **100** with dithiol **13**.

Table 4.2 Yields obtained from the preparation of 1,3-dithianes.

Entry ^a	100	Aldehyde R	Catalyst (equiv.) ^b	React. time (min)	98 Prod.	Yield (%) ^c
1	100a	Bn	I ₂ (0.1)	30	98a	53
2	100b	(CH ₂) ₃	BF ₃ · OEt ₂ (0.7)	90	98b	99
4	100c	TBDMSO-CH ₂	I ₂ (0.1)	30	98c	33
3	100d	<i>t</i> -Bu	NBS (0.1)	60	98d	62

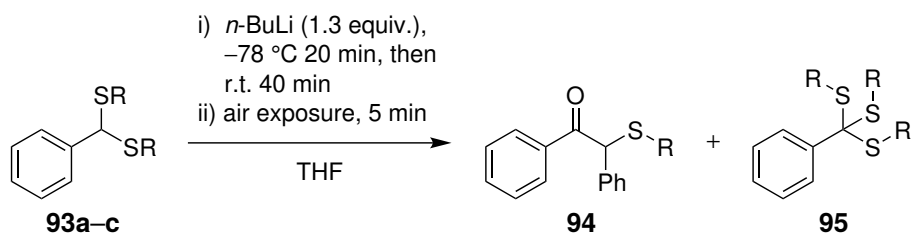
^a Unless otherwise noted, reactions were done in dry CH₂Cl₂ at room temperature. ^b Compared to aldehyde

^c Isolated yield.

In summary, a variety of dithioacetals and 1,3-dithianes were successfully prepared for the oxidation studies, which will be described in the following two sections. The choice of catalyst was an important factor in thioacetalization reactions. Based on the observations, iodine performs poorly as a catalyst for acyclic dithioacetals because the oxidation of thiols to disulfides competes with the thioacetalization. On the other hand, NBS was observed to be a versatile and easy to handle catalyst for thioacetalization, which provided generally good to excellent yields. However, as the goal of this study was not to optimize the yields of thioacetalizations, no strong conclusions can be made about the performance of the different catalyst due to the small amount of reactions.

4.2 Oxidation of Lithiated Dithioacetals

Acyclic dithioacetals **93a–c** were lithiated with *n*-butyl lithium according to the previously optimized procedure discussed in the section 3.3. Lithiated dithioacetals were oxidized by replacing the argon atmosphere with air for 2 or 5 minutes and then quenching the reaction by addition of saturated aqueous NH₄Cl (Scheme 4.3). The oxidation of **93a** afforded α -thioketone product **94a** in 48% yield after isolation (entry 1, Table 4.3). Orthothioester product **95a** could not be isolated because it co-eluted with the dithioacetal starting material in column chromatography. However, the characteristic peak for benzylic carbon in **95a** could be observed in ¹³C NMR spectrum indicating that the orthothioester formed in the reaction. The aerobic oxidation of **93b** gave a near quantitative yield of ketone **94a** and a good 72% yield of orthothioester **95b** (entry 2). Finally, the oxidation of dithioacetal **93c** gave ketone **94c** in 67% yield (entry 3). As with **95a**, the orthothioester **95c** could not be isolated from the crude reaction mixture. Nevertheless, a peak with characteristic chemical shift for the benzylic carbon of orthothioester could be observed in ¹³C NMR spectrum of the crude product. This indicates that the orthothioester was formed in the reaction.



Scheme 4.3 Aerobic oxidation of dithioacetals.

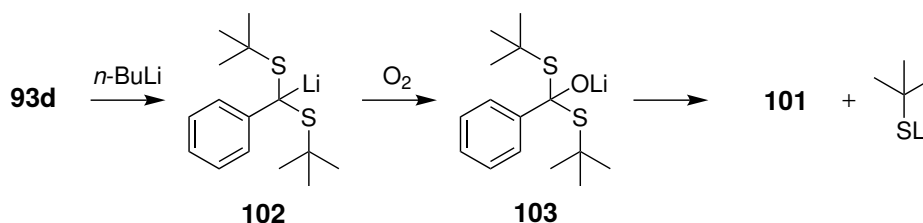
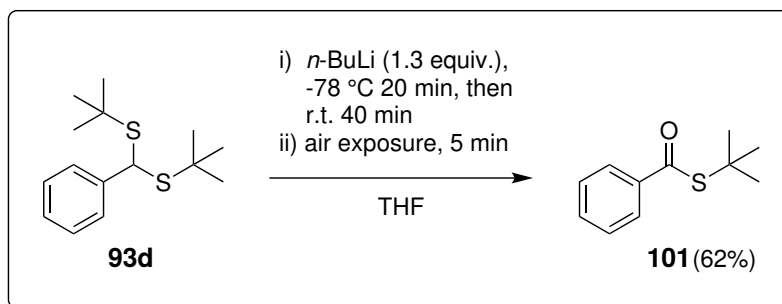
Table 4.3 Yields obtained from the aerobic oxidation of dithioacetals.

Entry	93	R	94	Yield (%) ^a	95	Yield (%) ^a
1 ^b	93a	Ph	94a	48	95a	– ^c
2	93b	<i>n</i> -Bu	94b	97	95b	72
3	93c	<i>sec</i> -Bu	94c	67	95c	– ^c

^a Isolated yield. ^b Exposed to air for 2 minutes ^c Observed in ¹H or ¹³C NMR, but not isolated

Dithioacetal **93b** was also oxidized by bubbling O₂ from a balloon into the reaction mixture through a long needle for 10 minutes. This afforded ketone **94b** in 41% yield and ortho-thioester **95b** in 80% yield after isolation by column chromatography. The same oxidation method was attempted with dithioacetals **93c–f**, but this was observed to be detrimental to the reaction as complex mixtures of products was observed to form by TLC analysis. Attempts to isolate products by column chromatography from the mixtures failed due to a large number of different compounds and small amounts of each compound present in the mixture. It is conceivable that the oxidation by bubbling O₂ to the reaction mixture leaves insufficient amount of lithiated dithioacetal to attack the thioester intermediate and the subsequent addition product. Caution should be used when O₂ is used in the oxidation as mixture of solvent vapor and oxygen was observed to ignite with a bright spark when a needle was inserted through a rubber septum protecting the reaction flask from atmosphere.

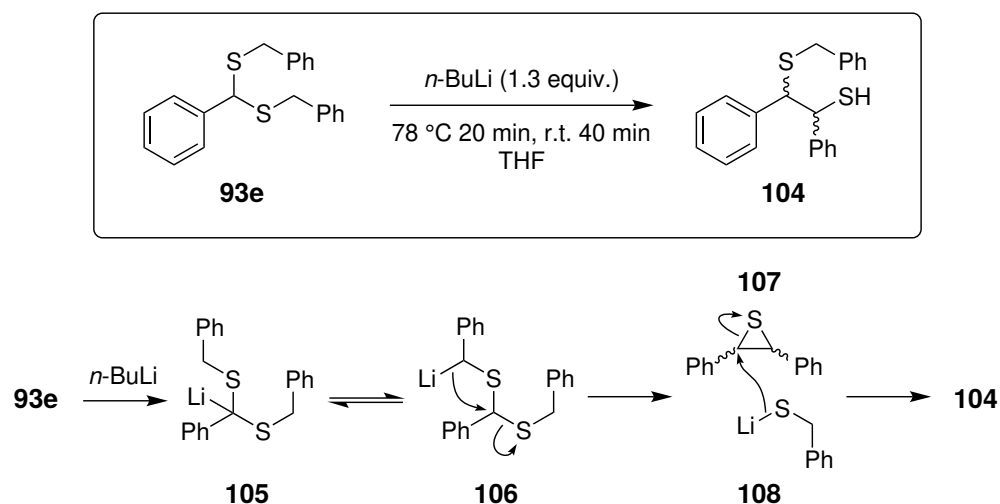
Interestingly, lithiation and subsequent oxidation of dithioacetal **93d** with air afforded starting material and thioester **101** (Scheme 4.4). This observation is in agreement with the hypothesized mechanism where lithiated dithioacetal **102** reacts with oxygen to produce lithium alkoxide **103**. Tetrahedral intermediate **103** then collapses to yield thioester **101** and lithium thiolate. In the hypothesized mechanism thioester would then undergo nucleophilic addition reaction with excess **102**. In this case the thioester and the lithiated dithioacetal are likely too sterically hindered to react any further due to bulky *tert*-butylthiol moieties. Likewise, steric hindrance could be also one possible factor causing the observed decrease in the yields of α -thio ketone products **94** when bulkier *sec*-butyl and phenyl substituted dithioacetals are used in the oxidation instead of primary *n*-butyl substituted dithioacetal. On the other hand, electronic effects such as possibly more efficient carbanion stabilization by phenyl substituent in lithiated **93a** can not be ruled out as a cause for decreasing yield.



Scheme 4.4 Aerobic oxidation of dithioacetal **93d**.

When lithiated dithioacetal **93e** was exposed to atmospheric air for 5 minutes before quenching the reaction, complete consumption of starting material and a single product could be observed on TLC. ¹H NMR of the crude reaction mixture confirmed the consumption of starting material and a formation of what was assumed to be a mixture of two diastereomers of an unknown product. Upon isolation of the unknown product by column chromatography a formation of white crystals was observed in some of the collected product fractions. Evaporation of solvent and recrystallization from hexane produced clean white crystals. ¹H and ¹³C NMR spectra of the crystals revealed that only one diastereomer had crystallized, while the supernatant contained the other diastereomer with a minor amount of uncrystallized diastereomer. The reaction was also conducted without exposing the lithiated dithioacetal to air before quenching the reaction at room temperature. ¹H and ¹³C NMR spectra of the crude reaction mixtures showed that the product composition was the same with or without the oxidation, which indicates that the formation of the products takes place prior to oxidation (Scheme 4.5).

¹H and ¹³C NMR spectra of isolated diastereomer corresponds well to the structure of **104**. Unfortunately, no previously published NMR spectrum of the compound **104** could be found to confirm the structure. In addition, compound corresponding to structure **104** could not be found in the mass spectrum of crystallized diastereomer. Because NMR spectra alone are not enough to prove that the isolated compound is **104**, further studies are still required to assign the structure of the isolated compound. For example, dithioacetal **93f** has been so far only oxidized with O₂, which resulted a complex mixture of products as discussed above. It would be interesting to see whether treatment of the dithioacetal **93f** with *n*-butyllithium would produce similar products as **104**.

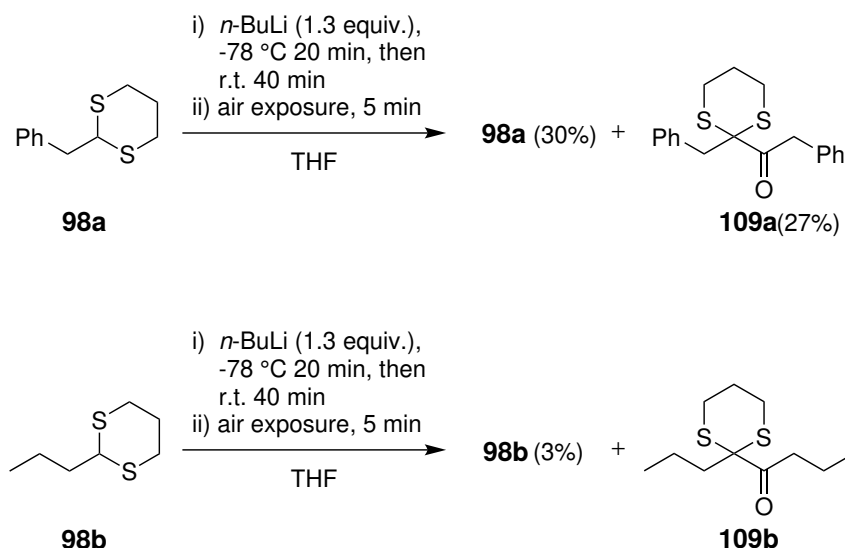


Scheme 4.5 Possible rearrangement of dithioacetal **93e**.

In summary, the oxidation of dithioacetals produced the expected α -thioketone product **94** and orthothioester product **95** when dithioacetals derived from phenyl, primary and secondary thiols were used. The reaction gave the best yields of products **94** and **95** when dithioacetal derived from primary thiol is used. Using dithioacetals derived from bulkier phenyl or secondary thiols decreased the yields, which is likely due to steric hindrance. When dithioacetal derived from tertiary thiol was used the reaction afforded a thioester. This observation gives information about the reaction mechanism as the obtained thioester is in accordance with the predicted polar mechanism. Finally, the dithioacetal derived from benzylic thiol **93e** produced an unexpected product upon treatment with *n*-butyllithium. The product could be a result of a novel anionic rearrangement, but more studies are needed to confirm this observation.

4.3 Oxidation of Lithiated 1,3-Dithianes

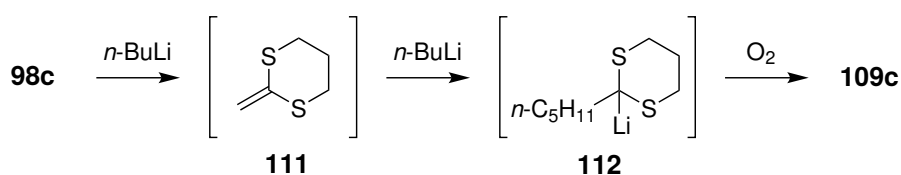
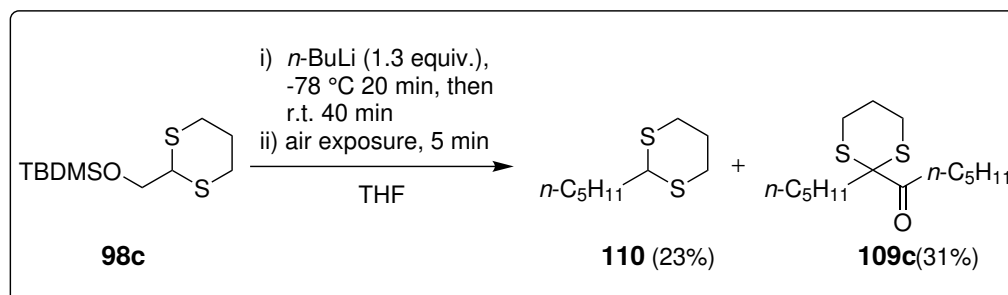
Oxidation of lithiated 1,3-dithianes **98a,b** afforded products **109a,b** and starting material (Scheme 4.6). Based on a TLC analysis of the crude reaction mixture, it is likely that more than 3% dithiane starting material **98b** was left from the oxidation, but due to volatility of the compound the yield decreased during workup and isolation. Despite of sampling multiple different solvent systems for mobile phase, product **109b** co-eluted with an unknown impurity in column chromatography and therefore could not be successfully isolated as a pure compound. Nonetheless, the structure of **109b** was resolved from ^1H and ^{13}C NMR spectra of the mixture. The procedure was later improved by my colleague and 24% yield of **109b** was obtained.



Scheme 4.6 Aerobic oxidation of dithianes **98a,b**.

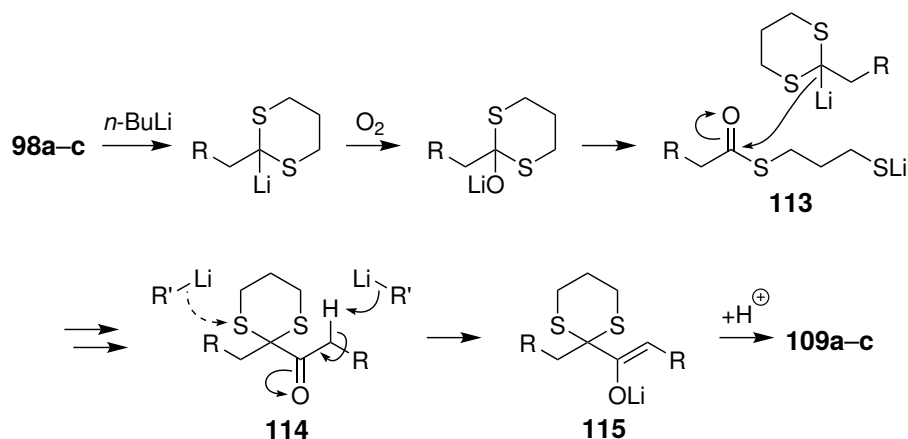
Dithiane **98a** was also lithiated with 2 equivalents of *n*-butyllithium prior oxidation in attempt to reduce starting material left from oxidation. After the oxidation and isolation of the products, 28% yield of **98a** and 22% yield of **109a** was obtained. It is likely that no more lithiated dithiane forms after the reaction is exposed to air as oxidation of *n*-butyllithium is much faster reaction than lithiation of dithiane.

Oxidation of dithiane derived from silyl protected hydroxyacetaldehyde **98c** afforded 23% yield of dithiane **110** and 31% yield of **109c**. Considering the structure of the products, it seems likely that dithiane **98c** undergoes elimination to give ketene thioacetal **111** [84]. Ketene thioacetal then further reacts with excess *n*-butyllithium to afford lithiated dithiane **112** [85]. Upon exposure to air, lithiated dithiane oxidizes yielding similar products than the previously discussed aliphatic dithianes **98a,b**.



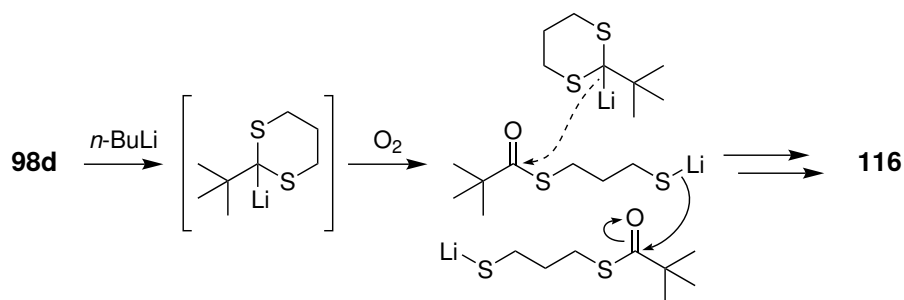
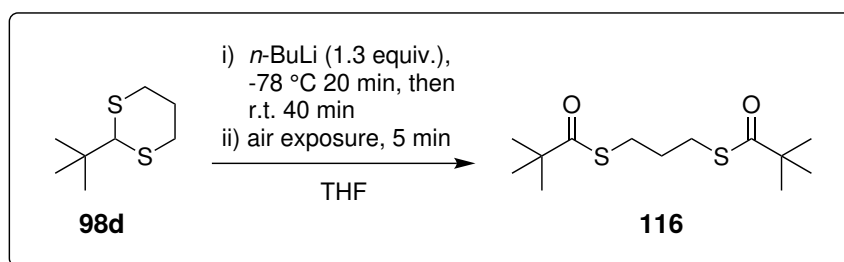
Scheme 4.7 Aerobic oxidation of dithiane **98c** and suggested intermediates leading to the product.

Based on the structure of the observed products, it is likely that the initial formation of the thioester intermediate **113** by oxidation of lithiated dithianes with alpha protons is followed by first nucleophilic attack by excess lithiated dithiane to form **114**. However, instead of the cleavage of the dithiane ring the reaction halts after this (Scheme 4.8). A probable explanation for the halting is that the deprotonation of carbon alpha to carbonyl (solid arrow) is faster than the nucleophilic attack to sulfur-carbon sigma bond (dashed arrow). After the formation of lithium enolate **115** the attack of lithiated dithiane to carbon-sulfur bond becomes unfavorable as this would lead to formation of a high energy dicarbanion.



Scheme 4.8 Suggested mechanism for oxidation of lithiated dithianes.

Aerobic oxidation of **98d** led to formation of thioester **116**. As with the acyclic dithioacetal **93d** derived from *tert*-butyl thiol, attack of the lithiated dithiane to thioester is probably too slow due to bulky *tert*-butyl groups (dashed arrow, Scheme 4.9) halting the oxidation to thioester intermediate. However, in this case lithium thiolate in the thioester is small enough to attack another thioester (solid arrow) to form the double thioester product **116**. The yield of slightly impure **116** was 7% after two attempts to separate it from byproduct by column chromatography. Based on the TLC taken from the crude reaction mixture after the workup, it seems likely that the amount of **116** has decreased during isolation, possibly due to hydrolysis of thioester group. Nevertheless, the structure of **116** could be resolved from ^1H and ^{13}C NMR spectra and a compound corresponding to the structure was also found by mass spectrometry. Repetition of the reaction by my colleague allowed isolation of **116** in 22% yield.



Scheme 4.9 Aerobic oxidation of dithiane **98d**.

In summary, the aerobic oxidation of 2-alkyl-2-lithio-1,3-dithianes with acidic protons alpha to the dithiane 2-carbon afforded compounds (**109a–c**). In the case of 1,3-dithiane derived from silyl protected hydroxyacetaldehyde, an initial elimination-addition reaction took place when the dithiane was treated with *n*-butyllithium. Due to the acidic alpha proton, competing formation of lithium enolate halted the reaction after lithiated 1,3-dithianes attacked the thioester intermediate. This gave more information about the mechanism of the oxidation because the observed products were in accordance with the intermediates formed in the initially suggested polar mechanism. Finally, the oxidation of lithiated 1,3-dithiane derived from pivaldehyde halted at thioester intermediate, which was likely due to bulky *tert*-butyl groups hindering the attack of lithiated dithiane to thioester.

5. CONCLUSIONS

The initial studies done in the organic synthesis laboratory at Tampere University of Technology had shown that upon exposure to air, 2-aryl-2-lithium-1,3-dithianes undergo autooxidative condensation forming previously unreported products in good yields. The purpose of this thesis was to evaluate if the scope of the autooxidative condensation could be extended to lithiated dithioacetals derived from benzaldehyde and cyclic 2-alkyl-2-lithio-1,3-dithianes. The study was performed by preparing the dithioacetals and 1,3-dithianes using modified procedures from literature and then oxidizing the lithiated substrates with air or pure oxygen. The oxidation was done by using the previously optimized oxidation procedure for 2-aryl-2-lithium-1,3-dithianes. The results of the oxidation reactions were then studied by isolating the products and by determining the structure and relative yield of each isolated product. The determination of the structures was done by using NMR and mass spectroscopy.

The starting material for the oxidation studies, dithioacetals derived from benzaldehyde and 2-alkyl-1,3-dithianes were successfully prepared by thioacetalization of aldehydes in moderate to excellent yields. Benzaldehyde was thioacetalized with phenyl, benzyl, primary, secondary and tertiary substituted thiols to evaluate how the substitution of thiol affects the oxidation of dithioacetals. Three primary 2-alkyl-1,3-dithianes and one tertiary 2-alkyl-1,3-dithiane were made to extend the scope of the oxidation to alkyl substituted dithianes. The choice of catalyst was observed to have a significant impact on yields of thioacetalizations. Iodine was observed to perform poorly as a catalyst for dithioacetals because the oxidation of thiols to disulfides competes with the thioacetalization. On the other hand, *N*-bromosuccinimide was found to be an excellent catalyst for the preparation of dithioacetals used in this thesis.

The aerobic oxidation of benzaldehyde dithioacetals derived from primary, secondary and benzene thiols yielded α -sulfide ketone and orthothioester products. The observed products were analogous to the previously observed products from the oxidation of the cyclic 2-aryl-2-lithium-1,3-dithianes, which indicates that the same autooxidative condensation reaction occurred with the aforementioned acyclic dithioacetals. An excellent 97% yield of α -sulfide ketone and a good yield of the corresponding orthothioester was obtained when dithioacetal derived from *n*-butylthiol was used. The yields of α -sulfide ketones decreased significantly when secondary or phenyl thiols were used instead, which is likely due to

increased steric hindrance compared to primary thiol. When dithioacetal derived from *tert*-butylthiol was used, the reaction afforded a thioester, S-(*tert*-butyl) benzothioate, in 62% yield. The observation indicates that the autooxidative process likely proceeds through a thioester intermediate and the bulkiness of *tert*-butyl group on thiol halts the reaction at this intermediate. Oxidation of the benzaldehyde dithioacetals with pure oxygen was observed to decrease yields and to lead to complex mixtures of products. No disulfide products similar to what Valiulin *et al.* reported [18] were observed, which suggest, although does not prove, that the mechanism of the reaction could be polar.

The aerobic oxidation of 2-alkyl-2-lithio-1,3-dithianes with protons alpha to the dithiane 2-carbon afforded products where the 1,3-dithiane protected aldehyde and the corresponding unprotected aldehyde had formed a bond between 2-carbon of the 1,3-dithiane and the carbonyl carbon of the aldehyde. While the yields of the dimeric products were poor, their structures gave more information about the reaction mechanism. A likely mechanistic explanation for the observed products is that a nucleophilic attack of an unoxidized 2-lithio-1,3-dithiane to the thioester intermediate is followed by formation of lithium enolate due to acidic proton alpha to carbonyl. The formation of the enolate halts the reaction by preventing the ring opening by another unoxidized 2-lithio-1,3-dithiane which would have led to the similar products obtained from the oxidation of 2-aryl-2-lithio-1,3-dithianes. As in the case of the dithioacetal derived from *tert*-butyl thiol, 2-*tert*-butyl substituted 1,3-dithiane also halted at the thioester intermediate.

Finally, the dithioacetal derived from benzylic thiol produced an unexpected product upon treatment with *n*-butyllithium. The product could be a result of an anionic rearrangement, in which the lithiated dithioacetal reacts intramolecularly to form a thiirane intermediate and a benzyl thiolate. The benzyl thiolate then opens the thiirane to form the product. However, more studies are needed to confirm this observation as the structure of the product has not been verified by mass spectrometry. The reaction could be studied by using substituted benzylic thiols in the dithioacetal. If the thiirane intermediate forms in the reaction it would be interesting to examine if other nucleophiles than thiolate could open the ring, for example, by adding excess of *n*-butyllithium.

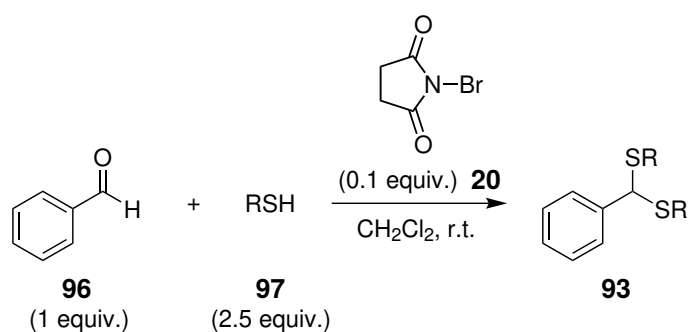
6. EXPERIMENTAL

6.1 General Remarks

Reactions were monitored by thin-layer chromatography (TLC) with commercial silica gel plates (Merck silica gel, 60 F₂₅₄). Visualization of the developed plates was performed under UV light at 254 nm and by staining with cerium ammonium molybdate, 2,4-dinitrophenylhydrazine and vanillin stains. Flash column chromatography was performed on silica gel 60 (40-63 μm) as stationary phase. Preparative TLC was conducted on Merck PLC glass plates with 1 mm thickness of silica gel 60 F₂₅₄ coating. ¹H NMR spectra were recorded at 300 MHz, ¹³C NMR spectra were recorded at 75 MHz in a 300 MHz Varian Mercury spectrometer, using CDCl₃ as solvent. Chemical shifts (δ) are reported in ppm referenced to the TMS peak (δ 0.00) for ¹H NMR and to CDCl₃ (δ 77.16) for ¹³C NMR. The following abbreviations are used to describe the peak splitting patterns: s = singlet, d = doublet, t = triplet, m = multiplet. High-resolution mass spectra were recorded on a Waters ESI-TOF MS spectrometer. Tetrahydrofuran (THF) was dried by distillation under argon with sodium metal and benzophenone as indicator. Dichloromethane (CH₂Cl₂) was dried by distillation under argon with calcium hydride.

6.2 Synthesis of Dithioacetals and 1,3-Dithianes

6.2.1 General Method A: NBS Catalysis

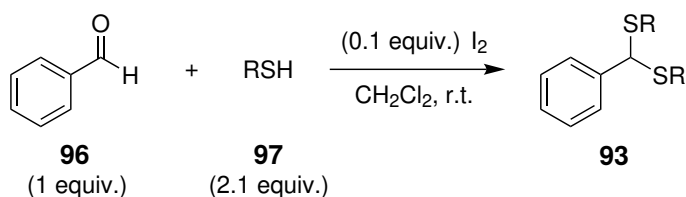


Scheme 6.1 General method for thioacetalization under NBS catalysis.

The procedure was modified from literature [42]. Benzaldehyde **96** (0.51 ml, 5 mmol, 1 equiv.) and *N*-bromosuccinimide **20** (89 mg, 0.5 mmol, 0.1 equiv.) were dissolved in dry

CH₂Cl₂ (25 ml). The solution was then stirred under argon at r.t. and thiol (12.5 mmol, 2.5 equiv.) was added dropwise. The reaction was monitored by TLC and quenched with 25 ml of 10% aqueous NaOH when the aldehyde was consumed (30-120 min). Aqueous and organic layers were separated and the aqueous layer was washed twice with 25 ml of CH₂Cl₂. The combined organic layers were washed with 25 ml brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product was then purified by recrystallization or flash chromatography.

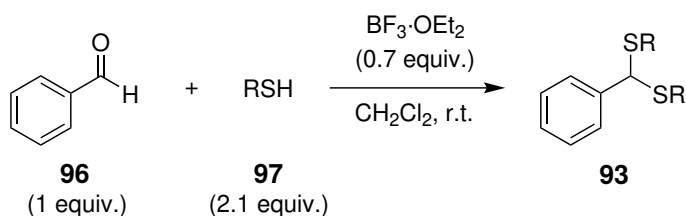
6.2.2 General Method B: I₂ Catalysis



Scheme 6.2 General method for thioacetalization under I₂ catalysis.

The procedure was modified from literature [36]. Benzaldehyde **96** (0.51 ml, 5 mmol, 1 equiv.) and thiol **97** (10.5 mmol, 2.1 equiv.) were dissolved in 25 ml of CH₂Cl₂. The solution was then stirred at r.t. and I₂ (0.13 g, 0.5 mmol, 0.1 equiv.) was added. The reaction was monitored by TLC. When the aldehyde was consumed (30–35 min) the reaction was quenched with 25 ml of 2% aqueous Na₂S₂O₃ and then washed with 25 ml of 10% aqueous NaOH. Aqueous and organic layers were separated and the aqueous layer was washed with 25 ml of CH₂Cl₂. The combined organic layers were washed with 25 ml of H₂O, dried over MgSO₄, filtered and concentrated under reduced pressure to yield the crude product. The crude product was then purified by recrystallization or flash chromatography.

6.2.3 General Method C: BF₃ · OEt₂ Catalysis

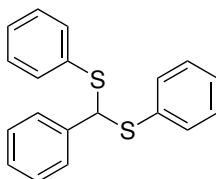


Scheme 6.3 General method for thioacetalization under BF₃ · OEt₂ catalysis.

The procedure was modified from literature [86]. Benzaldehyde **96** (0.51 ml, 5 mmol, 1 equiv.) and thiol **97** (10.5 mmol, 2.1 equiv.) were dissolved in 20 mL of dry CH₂Cl₂ under argon. The solution was stirred at room temperature and BF₃ · OEt₂ (0.43 mL, 3.5 mmol, 0.7

equiv.) was added dropwise. After the reaction was complete by TLC analysis, the reaction mixture was washed twice with 20 ml of 10% aqueous NaOH. The combined aqueous layers were then extracted twice with 20 mL of CH₂Cl₂. The organic layers were combined, washed with 25 mL of brine and dried over MgSO₄. The organic solvent was evaporated under reduced pressure and the product was then isolated by flash chromatography.

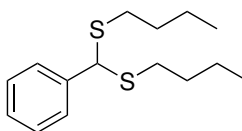
6.2.4 (Phenylmethylene)bis(phenylsulfane) (93a)



Scheme 6.4 (Phenylmethylene)bis(phenylsulfane) 93a

Method B, except CHCl₃ was used as a solvent. The reaction was quenched after 30 min and the product was isolated by recrystallization (hexane) to afford **93** as white crystals in 66% yield (1.011 g, 3.28 mmol). Obtained with the same spectral characterization as previously described [87]. ¹H NMR (300 MHz, CDCl₃): δ ppm 7.39-7.20 (m, 15H), 5.42 (s, 1H). Appendix 1.

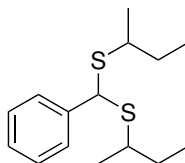
6.2.5 (Phenylmethylene)bis(butylsulfane) (93b)



Scheme 6.5 (Phenylmethylene)bis(butylsulfane) 93b

Method A. The reaction was quenched after 30 min and the product was isolated by flash chromatography (hexane/EtOAc 97.5/2.5) to afford **93b** as colorless oil in 91% yield (1.218 g, 4.54 mmol). ¹H NMR (300 MHz, CDCl₃): δ ppm 7.45-7.42 (m, 2H), 7.34-7.22 (m, 3H), 4.87 (s, 1H), 2.63-2.46 (m, 4H), 1.58-1.48 (m, 4H), 1.42-1.30 (m, 4H), 0.87 (t, J = 7.3 Hz, 6H). ¹³C NMR (75 MHz, CDCl₃): δ ppm 140.7, 128.5, 127.8, 127.8, 53.3, 32.0, 31.3, 22.1, 13.7. HR-MS (ESI) m/z calculated for C₁₅H₂₃S₂⁺ [M-H]⁺ 267.1236, found 267.1246. Appendices 2 and 3.

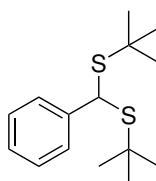
6.2.6 (Phenylmethylene)bis(sec-butylsulfane) (93c)



Scheme 6.6 (Phenylmethylene)bis(sec-butylsulfane) 93c

Method A. The reaction was quenched after 30 min and the product was isolated by flash chromatography (hexane/EtOAc 98/2) to afford **93c** as light yellow oil in 86% yield (1.150 g, 4.29 mmol). ^1H NMR (300 MHz, CDCl_3): δ ppm 7.47 (d, $J = 7.6$ Hz, 2H), 7.34-7.22 (m, 3H), 4.94 (s, 1H), 2.88-2.63 (m, 2H), 1.66-1.42 (m, 4H), 1.24-1.20 (m, 6H), 0.97-0.88 (m, 6H). ^{13}C NMR (75 MHz, CDCl_3): δ ppm 141.3, 128.6, 127.9, 127.8, 50.9, 50.7, 42.6, 42.5, 29.7, 29.6, 20.8, 20.8, 20.7, 11.3, 11.3. HR-MS (ESI) m/z calculated for $\text{C}_{15}\text{H}_{23}\text{S}_2^+$ $[\text{M-H}]^+$ 267.1236, found 267.1444. Appendices 4 and 5.

6.2.7 (Phenylmethylene)bis(tert-butylsulfane) (93d)

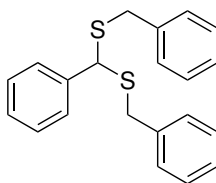


Scheme 6.7 (Phenylmethylene)bis(tert-butylsulfane) 93d

Method A, except 0.2 equivalents of NBS was initially used and additional 0.1 equivalents of NBS was added after 80 min. The reaction was quenched after 120 min and the product **93d** obtained as pure white solid after drying in vacuum over night. 87% yield (1.171 g, 4.37 mmol). ^1H NMR (300 MHz, CDCl_3): δ ppm 7.48-7.44 (m, 2H), 7.32-7.26 (m, 2H), 7.23-7.18 (m, $J = 1.3$ Hz, 1H), 5.02 (s, 1H), 1.29 (s, 18H). ^{13}C NMR (75 MHz, CDCl_3): δ ppm 144.1, 128.7, 127.7, 127.4, 48.8, 45.8, 31.3. HR-MS (ESI) m/z calculated for $\text{C}_{15}\text{H}_{24}\text{S}_2\text{Na}^+$ $[\text{M}+\text{Na}]^+$ 291.1212, found 291.1251. Appendices 6 and 7.

Method C. The reaction was quenched after 2 h and the product was isolated by flash chromatography (hexane/EtOAc 97.5/2.5) to afford **93d** as white solid in 25% yield (335 mg, 1.25 mmol).

6.2.8 (Phenylmethylene)bis(benzylsulfane) (93e)

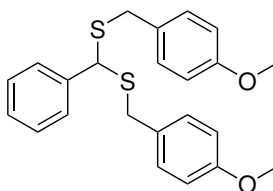


Scheme 6.8 (Phenylmethylene)bis(benzylsulfane) **93e**

Method A, except additional 0.1 equivalents of NBS was added after 45 min. The reaction was scaled up so that 10 mmol of benzaldehyde was used. The reaction was quenched after 80 min and the product was isolated by recrystallization (*i*PrOH) to afford **93e** as white crystals in 96% yield (3.217 g, 9.56 mmol). Obtained with the same spectral characterization as previously described [87]. ¹H NMR (300 MHz, CDCl₃) δ ppm 7.35-7.16 (m, 15H), 4.47 (s, 1H), 3.77 (d, J = 13.5 Hz, 2H), 3.55 (d, J = 13.5 Hz, 2H). Appendix 8.

Method B. The reaction was quenched after 35 min. Recrystallization from *i*PrOH or hexane yielded a mixture of the product and a byproduct. The product was isolated by flash chromatography (hexane/EtOAc 97.5/2.5) to afford **93e** as white crystals in 47% yield (798 mg, 2.37 mmol).

6.2.9 (Phenylmethylene)bis((4-methoxybenzyl)sulfane) (93f)

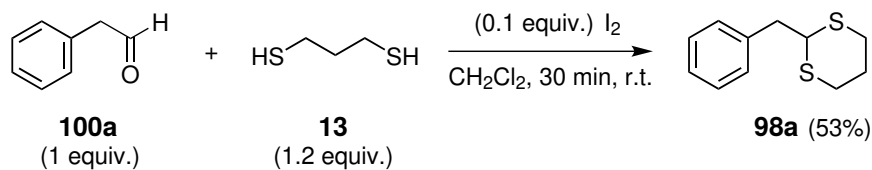


Scheme 6.9 (Phenylmethylene)bis(benzylsulfane) **93f**

Method A, except 0.2 equivalents of NBS was used. The reaction was quenched after 70 min and the product and the product was isolated by recrystallization (*i*PrOH/hexane) to afford **93f** as white crystals in 99% yield (1,9673 g, 4.96 mmol). ¹H NMR (300 MHz, CDCl₃) δ ppm 7.32-7.24 (m, 5H), 7.08-7.05 (m, 4H), 6.80-6.76 (m, 4 H), 4.43 (s, 1 H), 3.80 (s, 6H), 3.73 (d, J = 13.5 Hz, 2H), 3.50 (d, J = 13.5 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃) δ ppm 158.7, 139.8, 130.2, 129.8, 128.7, 128.2, 128.0, 114.0, 55.4, 50.7, 36.0. Appendices 9 and 10.

Method B. The reaction was quenched after 30 min. Recrystallization from *i*PrOH and then from hexane yielded a mixture of the product and a byproduct. The product was isolated by flash chromatography (hexane/EtOAc 90/10) to afford **93f** as white crystals in 22% yield (441 mg, 1.11 mmol).

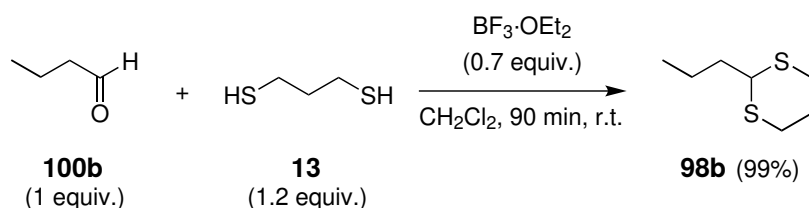
6.2.10 2-Benzyl-1,3-dithiane (98a)



Scheme 6.10 Synthesis of 2-Benzyl-1,3-dithiane **98a**

Method B, except 1 equivalent (616 mg, 5 mmol) of 2-phenylacetaldehyde **100a** and 1.2 equivalents (0.6 ml, 6 mmol) of propane-1,3-dithiol **13** were used. The reaction was quenched after 30 min and the product was isolated by flash chromatography (hexane/EtOAc 85/15) to afford **98a** as pale green solid in 53% yield (560 mg, 2.66 mmol). Obtained with the same spectral characterization as previously described [88]. ^1H NMR (300 MHz, CDCl_3): δ ppm 7.34-7.22 (m, 5H), 4.24 (t, $J = 7.3$ Hz, 1H), 3.02 (d, $J = 7.3$ Hz, 2H), 2.85-2.80 (m, 4H), 2.15-2.05 (m, 1H), 1.92-1.79 (m, 1H). Appendix 11.

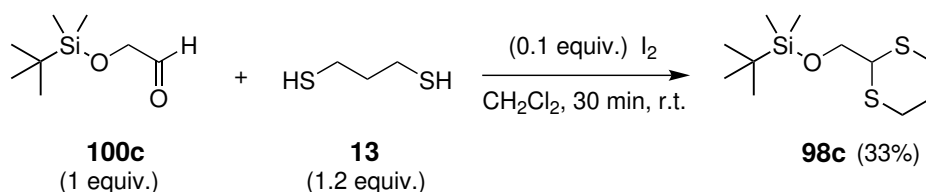
6.2.11 2-Propyl-1,3-dithiane (98b)



Scheme 6.11 Synthesis of 2-Propyl-1,3-dithiane **98b**

Method C, except 1 equivalent (0.45 ml, 5 mmol) of butyraldehyde **100b** and 1.2 equivalents (0.6 ml, 6 mmol) of propane-1,3-dithiol **13** were used. The reaction was quenched after 90 min and the product was isolated by flash chromatography (hexane/EtOAc 85/15) to afford **98b** as colorless oil in 99% yield (808 mg, 4.98 mmol). Obtained with same spectral characterization as previously described [43]. ^1H NMR (300 MHz, CDCl_3): δ ppm 4.05 (t, $J = 6.7$ Hz, 1H), 2.92-2.76 (m, 4H), 2.14-2.06 (m, 1H), 1.90-1.77 (m, 1H), 1.75-1.67 (m, 2H), 1.59-1.45 (m, 2H), 0.85-0.97 (m, 3H). Appendix 12.

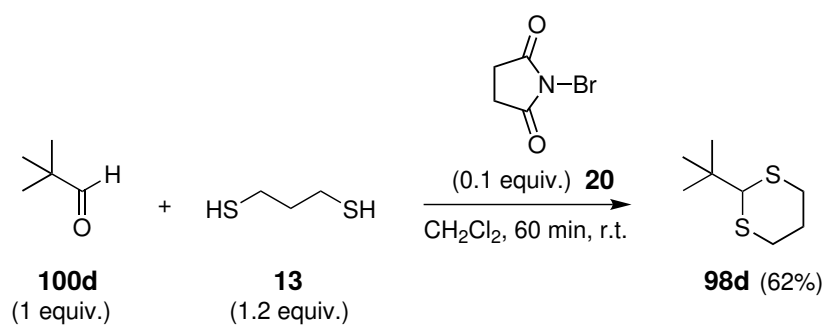
6.2.12 ((1,3-Dithian-2-yl)methoxy)(tert-butyl)dimethylsilane (**98c**)



Scheme 6.12 Synthesis of ((1,3-Dithian-2-yl)methoxy)(tert-butyl)dimethylsilane **98c**

Method B, except 1 equivalent (616 mg, 5 mmol) of 2-((tert-butyl)dimethylsilyloxy)acetaldehyde **100c** and 1.2 equivalents (0.6 ml, 6 mmol) of propane-1,3-dithiol **13** were used. The reaction was quenched after 30 min and the product was isolated by flash chromatography (hexane/EtOAc, gradient from 85/15 to 60/40) to afford **98c** as colorless oil in 33% yield (433 mg, 1.64 mmol). ^1H NMR (300 MHz, CDCl_3): δ ppm 4.13 (t, $J = 6.5$ Hz, 1H), 3.86 (d, $J = 6.4$ Hz, 2H), 2.91-2.76 (m, 4H), 2.16-2.07 (m, 1H), 1.97-1.85 (m, 1H), 0.91 (s, 9H), 0.10 (s, 6H). ^{13}C NMR (75 MHz, CDCl_3): δ ppm 66.1, 48.6, 29.1, 26.2, 26.0, 18.6, -5.2. HR-MS (ESI) m/z calculated for $\text{C}_{11}\text{H}_{24}\text{OS}_2\text{SiNa}^+$ $[\text{M}+\text{Na}]^+$ 287.0930, found 287.0953. Appendices 13 and 14.

6.2.13 2-(Tert-butyl)-1,3-dithiane (**98d**)



Scheme 6.13 Synthesis of 2-(Tert-butyl)-1,3-dithiane **98d**

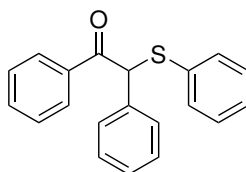
Method A, except 1 equivalent (0.54 ml, 5 mmol) of pivaldehyde **100d** and 1.2 equivalents (0.6 ml, 6 mmol) of propane-1,3-dithiol **13** were used. The reaction was quenched after 60 min and the product **98d** was obtained as pure white solid after drying in vacuum over night. 62% yield (544 mg, 3.08 mmol). Obtained with same spectral characterization as previously described [43]. ^1H NMR (300 MHz, CDCl_3): δ ppm 4.00 (s, 1H), 2.91-2.87 (m, 4H), 2.11-2.04 (m, 1H), 1.85-1.75 (m, 1H), 1.12 (s, 9H). Appendix 15.

6.3 Oxidation of Lithiated Dithioacetals and 1,3-Dithianes

6.3.1 General Method for the Aerobic Oxidation

Dithioacetal or dithiane (1 mmol, 1 equiv.) was dissolved in dry THF (5 ml) under argon. The solution was stirred and cooled to $-78\text{ }^{\circ}\text{C}$ in an acetone/liquid nitrogen bath and *n*-BuLi (1.3 equiv.) solution in hexane was added dropwise to the reaction mixture. The reaction was left in the cold bath for 20 minutes, after which the cold bath was removed and the reaction was let to warm at room temperature for 40 minutes. The argon balloon was replaced with an atmospheric air balloon and a venting needle was inserted in the septum to allow air flow above the surface of the solution. After 5 minutes, the solution was quenched with 10 ml of saturated aqueous NH_4Cl . 10 ml of Et_2O was added and the aqueous and organic layers were separated. The aqueous phase was extracted twice with 10 ml of Et_2O . The organic phases were combined and dried over MgSO_4 . The reaction mixture was then concentrated under reduced pressure and the products were isolated by flash chromatography.

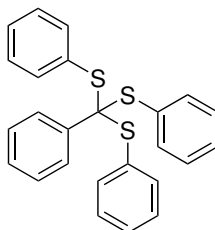
6.3.2 1,2-Diphenyl-2-(phenylthio)ethan-1-one (94a)



Scheme 6.14 1,2-Diphenyl-2-(phenylthio)ethan-1-one **94a**

After the aerobic oxidation of dithioacetal **93a**, **94a** was isolated by flash chromatography (hexane/EtOAc 97.5/2.5). 48% yield (97 mg, 0.32 mmol), white solid. ^1H NMR (300 MHz, CDCl_3): δ ppm 7.94-7.90 (m, 2H), 7.49-7.44 (m, 1H), 7.38-7.17 (m, 12H), 5.85 (s, 1H). ^{13}C NMR (75 MHz, CDCl_3): δ ppm 194.8, 136.6, 135.6, 134.1, 133.4, 133.1, 129.0, 128.9, 128.8, 128.7, 128.1, 128.0, 60.4. HR-MS (ESI) m/z calculated for $\text{C}_{20}\text{H}_{17}\text{OS}^+$ $[\text{M}+\text{H}]^+$ 305.0995, found 305.1013. Appendices 16 and 17.

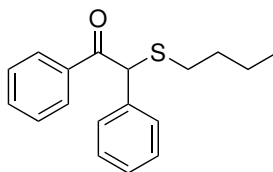
6.3.3 (Phenylmethanetriyl)tris(phenylsulfane) (**95a**)



Scheme 6.15 (Phenylmethanetriyl)tris(phenylsulfane) 95a

After the aerobic oxidation of dithioacetal **93a**, orthothioester **95a** could not be isolated due to low polarity and structural similarity to **93a**. However, the following characteristic peaks for **95a** can be observed from the NMR spectrum of a mixture with the dithioacetal **93a**. ^{13}C NMR (75 MHz, CDCl_3): δ ppm 139.4, 132.9, 128.8, 128.4, 128.3, 128.0, 127.9, 77.0. Appendix 18.

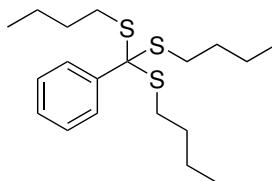
6.3.4 2-(Butylthio)-1,2-diphenylethan-1-one (**94b**)



Scheme 6.16 2-(Butylthio)-1,2-diphenylethan-1-one 94b

After the aerobic oxidation of dithioacetal **93b**, **94b** was isolated by flash chromatography (hexane/EtOAc 95/5). 97% yield (92 mg, 0.32 mmol), white solid. ^1H NMR (300 MHz, CDCl_3): δ ppm 7.99-7.96 (m, 2H), 7.53-7.23 (m, 8H), 5.55 (s, 1H), 2.56-2.42 (m, 2H), 1.58-1.48 (m, 2H), 1.41-1.29 (m, 2H), 0.85 (t, $J = 7.3$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ ppm 195.3, 136.9, 135.9, 133.3, 129.0, 128.9, 128.9, 128.7, 128.0, 55.5, 31.3, 31.2, 22.1, 13.7. HR-MS (ESI) m/z calculated for $\text{C}_{18}\text{H}_{21}\text{OS}^+$ $[\text{M}+\text{H}]^+$ 285.1308, found 285.1328. Appendices 19 and 20.

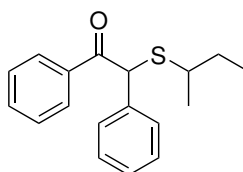
6.3.5 (Phenylmethanetriyl)tris(butylsulfane) (95b)



Scheme 6.17 (Phenylmethanetriyl)tris(butylsulfane) **95b**

After the aerobic oxidation of dithioacetal **93b**, orthothioester **95b** was isolated by flash chromatography (hexane/EtOAc 95/5). 72% yield (86 mg, 0.24 mmol), colorless oil. ^1H NMR (300 MHz, CDCl_3): δ ppm 7.87-7.84 (m, 2H), 7.35-7.21 (m, 3H), 2.58 (t, $J = 7.3$ Hz, 6H), 1.51-1.29 (m, 12H), 0.88-0.83 (m, 9H). ^{13}C NMR (75 MHz, CDCl_3): δ ppm 141.8, 131.3, 127.9, 127.6, 73.5, 31.5, 30.5, 22.3, 13.7. HR-MS (ESI) m/z calculated for $\text{C}_{15}\text{H}_{23}\text{S}_3^+$ [$\text{M}-\text{ceS}(\text{CH}_2)_3\text{CH}_3$] $^+$ 267.1236, found 267.1255. Appendices 21 and 22.

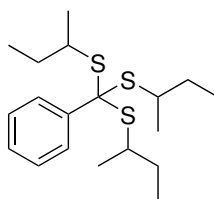
6.3.6 2-(Sec-butylthio)-1,2-diphenylethan-1-one (94c)



Scheme 6.18 2-(Sec-butylthio)-1,2-diphenylethan-1-one **94c**

After the aerobic oxidation of dithioacetal **93c**, **94c** was isolated as a 1:1 mixture of diastereomers by flash chromatography (hexane/ Et_2O 95/5). 67% yield (63 mg, 0.22 mmol), pale yellow solid. 1:1 mixture of diastereomers. ^1H NMR (300 MHz, CDCl_3): δ ppm 8.01-7.97 (m, 4H), 7.54-7.23 (m, 16H), 5.60 (s, 2H), 2.75-2.61 (m, 2H), 1.72-1.42 (m, 4H), 1.30 (d, $J = 6.4$ Hz, 3H), 1.19 (d, $J = 7.0$ Hz, 3H), 0.98-0.86 (m, 6H). ^{13}C NMR (75 MHz, CDCl_3): δ ppm 195.5, 195.4, 137.2, 135.9, 133.3, 129.0, 128.9, 128.9, 128.7, 127.9, 54.7, 54.6, 42.1, 41.9, 29.7, 29.7, 21.0, 20.6, 11.3, 11.2. HR-MS (ESI) m/z calculated for $\text{C}_{18}\text{H}_{21}\text{OS}^+$ [$\text{M}+\text{H}$] $^+$ 285.1308, found 285.1303. Appendices 23 and 24.

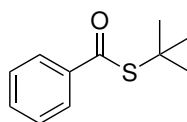
6.3.7 (Phenylmethanetriyl)tris(sec-butylsulfane) (95c)



Scheme 6.19 (Phenylmethanetriyl)tris(sec-butylsulfane) **95c**

After the aerobic oxidation of dithioacetal **93c**, orthothioester **95c** could not be isolated due to low polarity and structural similarity to **93c**. However, the following characteristic peaks for **95c** can be observed in NMR spectrum of the crude reaction mixture. ^{13}C NMR (75 MHz, CDCl_3): δ ppm 69.3, 29.0 20.1, 11.5. Appendix 25.

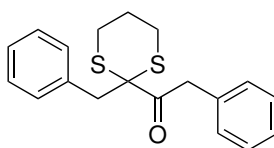
6.3.8 S-(tert-butyl) benzothioate (101)



Scheme 6.20 S-(tert-butyl) benzothioate **101**

After the aerobic oxidation of dithioacetal **93d**, **101** was isolated by preparative TLC (TLC plate was eluted five times with pentane). 62% yield (60 mg, 0.31 mmol). Obtained with same spectral characterization as previously described [89]. ^1H NMR (300 MHz, CDCl_3): δ ppm 7.93-7.90 (m, 2H), 7.56-7.51 (m, $J = 7.3$ Hz, 1H), 7.44-7.39 (m, 2H), 1.58 (s, 9H). Appendix 26.

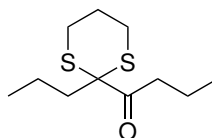
6.3.9 1-(2-Benzyl-1,3-dithian-2-yl)-2-phenylethan-1-one (109a)



Scheme 6.21 1-(2-Benzyl-1,3-dithian-2-yl)-2-phenylethan-1-one **109a**

After the aerobic oxidation of dithiane **98a**, **109a** was isolated by flash chromatography (hexane/EtOAc 95/5). 27% yield (45 mg, 0.14 mmol), white solid. ^1H NMR (300 MHz, CDCl_3): δ ppm 7.33-7.21 (m, 10H), 4.00 (s, 2H), 3.41 (s, 2H), 2.86-2.76 (m, 2H), 2.60-2.53 (m, 2H), 1.99-1.90 (m, 1H), 1.84-1.73 (m, 1H). ^{13}C NMR (75 MHz, CDCl_3): δ ppm 200.6, 134.9, 134.3, 130.2, 129.9, 128.5, 128.5, 127.7, 127.0, 62.5, 44.3, 43.4, 28.0, 24.2. HR-MS (ESI) m/z calculated for $\text{C}_{19}\text{H}_{21}\text{OS}_2^+$ $[\text{M}+\text{H}]^+$ 329.1028, found 329.1052. Appendices 27 and 28.

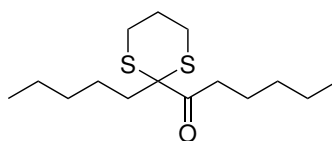
6.3.10 1-(2-Propyl-1,3-dithian-2-yl)butan-1-one (109b)



Scheme 6.22 1-(2-Propyl-1,3-dithian-2-yl)butan-1-one **109b**

After the aerobic oxidation of dithiane **98b**, a mixture of **109b** and an unknown byproduct was isolated by flash chromatography (hexane/CH₂Cl₂ 55/45). However, the following characteristic peaks for **109b** can be observed from the NMR spectrum of the mixture. ¹³C NMR (75 MHz, CDCl₃): δ ppm 204.3, 61.4, 40.6, 37.8, 27.9, 25.0, 18.4, 18.0, 14.5, 14.0. HR-MS (ESI) m/z calculated for C₁₁H₂₁OS₂⁺ [M+H]⁺ 233.1028, found 233.1050. Appendix 29.

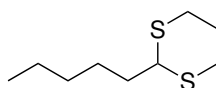
6.3.11 1-(2-Pentyl-1,3-dithian-2-yl)hexan-1-one (109c)



Scheme 6.23 1-(2-Pentyl-1,3-dithian-2-yl)hexan-1-one **109c**

After the aerobic oxidation of dithiane **98c**, **109c** was isolated by flash chromatography (hexane/CH₂Cl₂ gradient from 85/15 to 60/40). 31% yield (44 mg, 0.13 mmol), colorless oil. ¹H NMR (300 MHz, CDCl₃): δ ppm 3.02-2.92 (m, 2H), 2.67-2.57 (m, 4H), 2.07-2.01 (m, 1H), 1.97-1.92 (m, 2H), 1.87-1.71 (m, 1H), 1.66-1.57 (m, 2H), 1.42-1.28 (m, 10H), 0.90-0.83 (m, 6H). ¹³C NMR (75 MHz, CDCl₃): δ ppm 204.5, 61.5, 38.5, 35.8, 32.1, 31.6, 27.9, 25.0, 24.7, 24.1, 22.6, 22.3, 14.1, 14.0. HR-MS (ESI) m/z calculated for C₁₅H₂₉OS₂⁺ [M+H]⁺ 289.1654, found 289.1676. Appendices 30 and 31.

6.3.12 2-pentyl-1,3-dithiane (110)

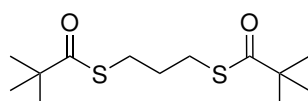


Scheme 6.24 2-pentyl-1,3-dithiane **110**

After the aerobic oxidation of dithiane **98c**, dithiane **110** was isolated by flash chromatography (hexane/CH₂Cl₂ gradient from 85/15 to 60/40). 23% yield (44 mg, 23 mmol),

colorless oil. Obtained with same spectral characterization as previously described [90]. ^1H NMR (300 MHz, CDCl_3): δ ppm 4.03 (t, $J=7.0$ Hz, 1H), 2.91-2.76 (m, 4H), 2.14-2.06 (m, 1H), 1.91-1.79 (m, 1H), 1.76-1.68 (m, 2H), 1.54-1.44 (m, 2H), 1.32-1.24 (m, 4H), 0.89-0.85 (m, 3H). Appendix 32.

6.3.13 *S,S'*-(propane-1,3-diyl) bis(2,2-dimethylpropanethioate) (116)

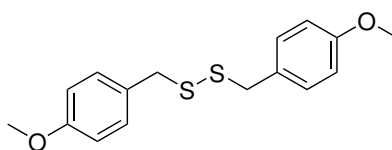


Scheme 6.25 *S,S'*-(propane-1,3-diyl) bis(2,2-dimethylpropanethioate) **116**

After the aerobic oxidation of dithiane **98d**, thioester **116** was isolated by flash chromatography (hexane/ CH_2Cl_2 gradient from 70/30 to 65/35, then second column hexane/EtOAc 97/3). ^1H NMR (300 MHz, CDCl_3): δ ppm 2.89 (t, $J = 7.0$ Hz, 4H), 1.82 (quin, $J = 7.0$ Hz, 2H), 1.23 (s, 18H). ^{13}C NMR (75 MHz, CDCl_3): δ ppm 206.7, 46.6, 29.7, 27.6, 27.5. HR-MS (ESI) m/z calculated for $\text{C}_{13}\text{H}_{25}\text{O}_2\text{S}_2^+$ $[\text{M}+\text{H}]^+$ 277.1290, found 277.1323. Appendices 33 and 34.

6.4 Other products

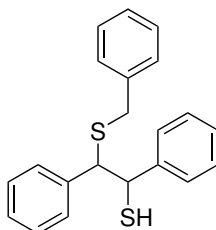
6.4.1 1,2-Bis(4-methoxybenzyl)disulfane (99)



Scheme 6.26 1,2-Bis(4-methoxybenzyl)disulfane **99**

When **93f** was synthesized with iodine catalyst (Section 6.2.9), a byproduct was obtained as a white solid after the isolation by column chromatography. It was later identified as 1,2-bis(4-methoxybenzyl)disulfane **99** by NMR spectroscopy. 7% yield calculated from the thiol (111 mg, 0.36 mmol). Obtained with same spectral characterization as previously described [91]. ^1H NMR (300 MHz, CDCl_3) δ ppm 7.18-7.14 (m, 4H), 6.87-6.83 (m, 4H), 3.76 (s, 6H), 3.58 (s, 4H). Appendix 35.

6.4.2 2-(Benzylthio)-1,2-diphenylethane-1-thiol (104)



Scheme 6.27 2-(Benzylthio)-1,2-diphenylethane-1-thiol **104**

After the aerobic oxidation of dithioacetal **93e**, the product with a suggested structure **104** was isolated by flash chromatography (hexane/EtOAc 7,5/2,5). The yield of the mixture of diastereomers **104** was 71% (477 mg, 1.42 mmol). A single diastereomer was isolated by recrystallization (hexane) with the following NMR spectra: ^1H NMR (300 MHz, CDCl_3) δ ppm 7.36-7.03 (m, 15H), 4.41 (dd, $J = 3.5, 10.5$ Hz, 1H), 4.02 (d, $J = 10.5$ Hz, 1H), 3.23-3.16 (m, 2H), 1.87 (d, $J = 3.5$ Hz, 1H). ^{13}C NMR (75MHz, CDCl_3) δ ppm 141.0, 140.3, 137.6, 129.1, 128.9, 128.7, 128.6, 128.4, 128.1, 128.0, 128.0, 127.1, 56.6, 49.6, 36.5. Appendices 36 and 37.

The same product composition was observed by TLC and ^1H NMR when the standard procedure was used, but the reaction was quenched with saturated aqueous NH_4Cl without exposing to air, which indicates that the observed products form upon treatment of lithiated dithioacetal **93e** with *n*-butyllithium.

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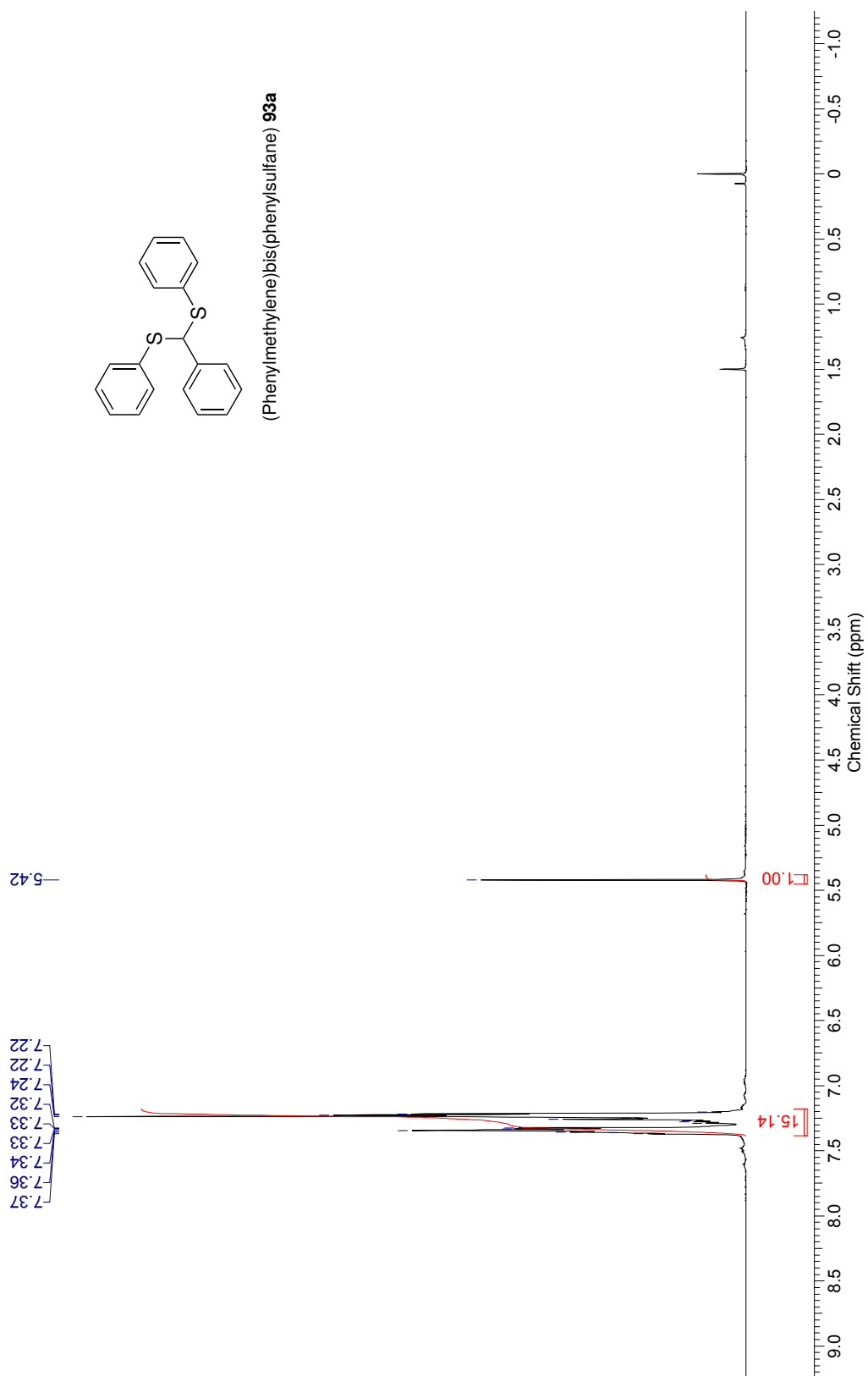
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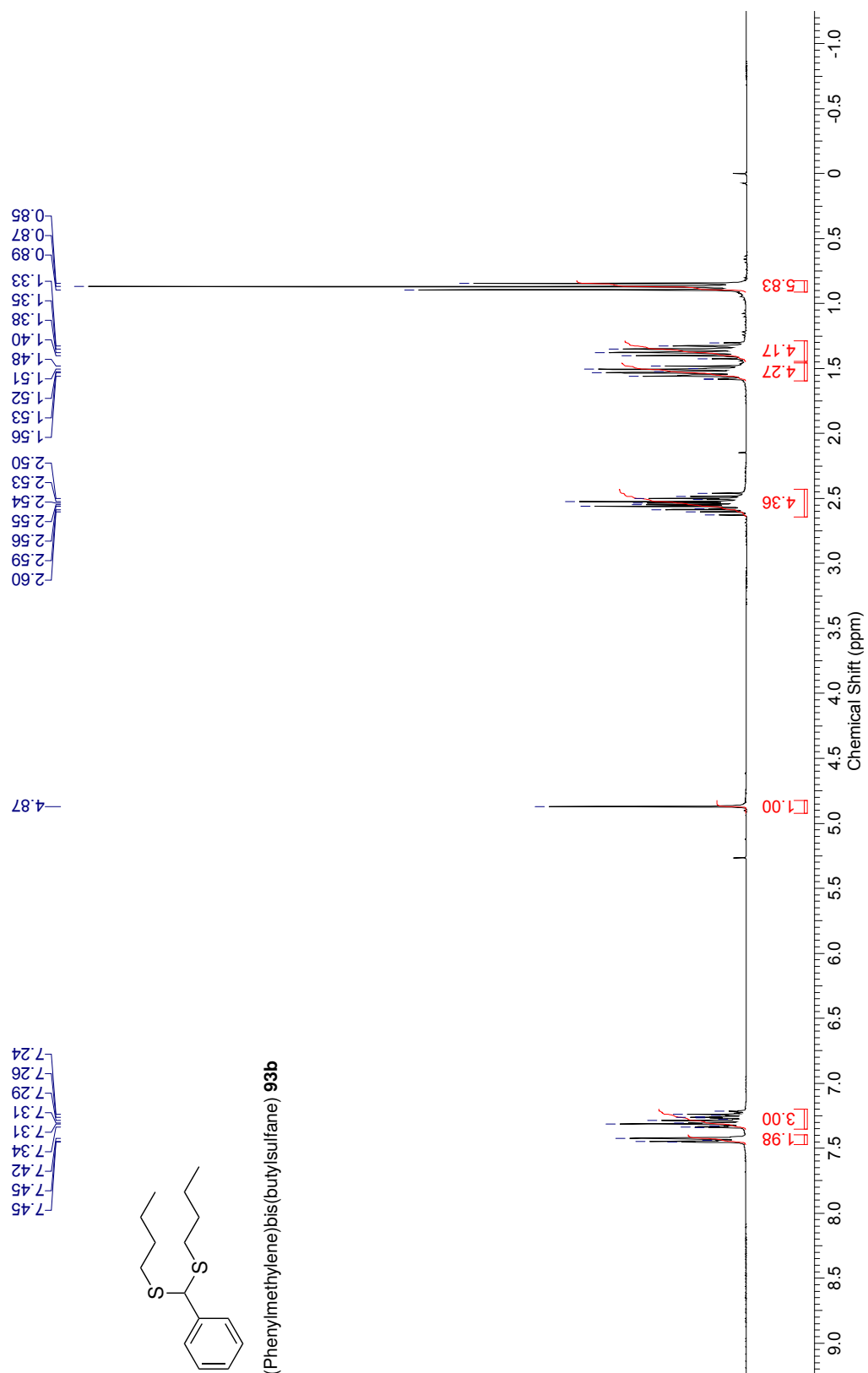
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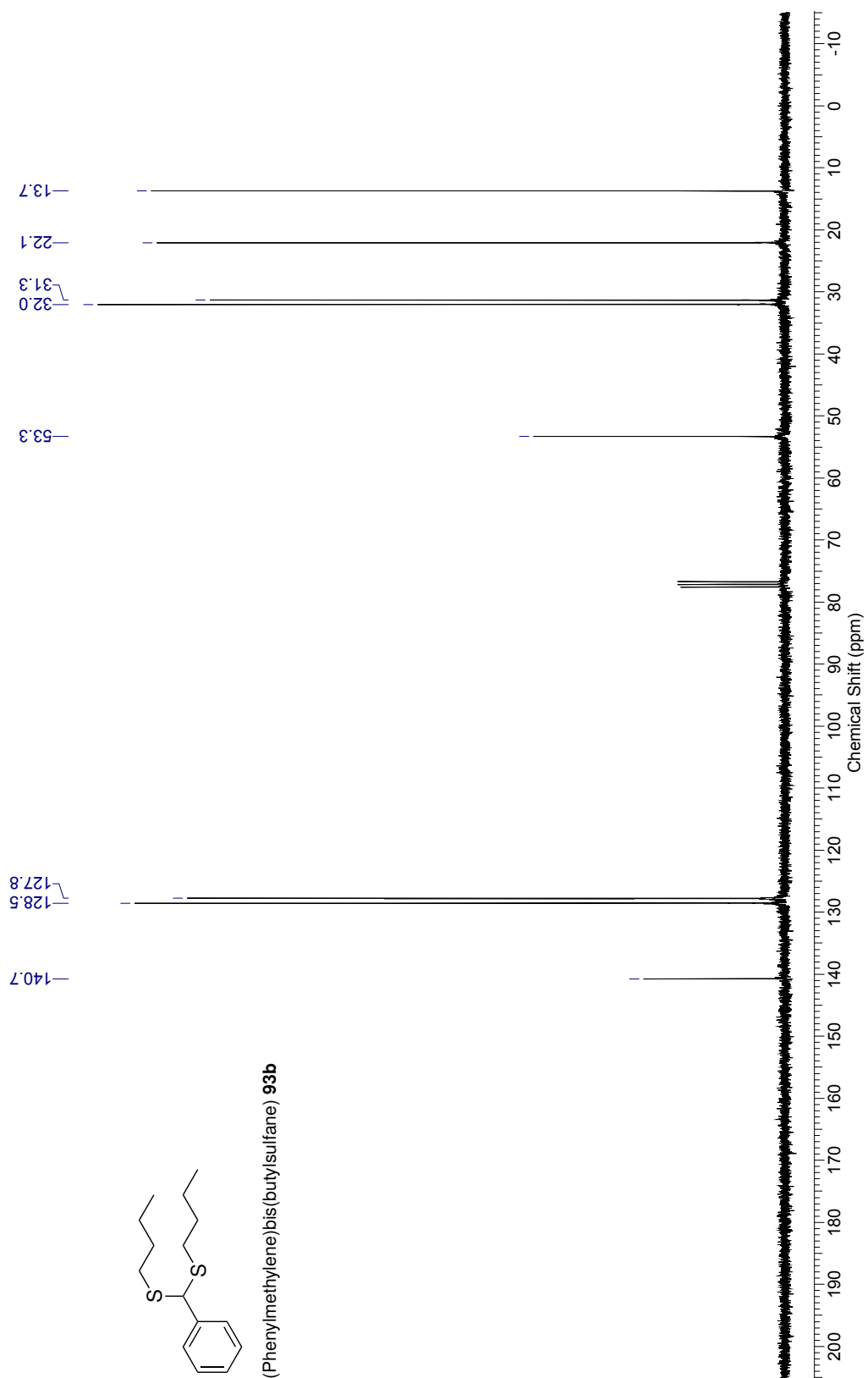
APPENDICES

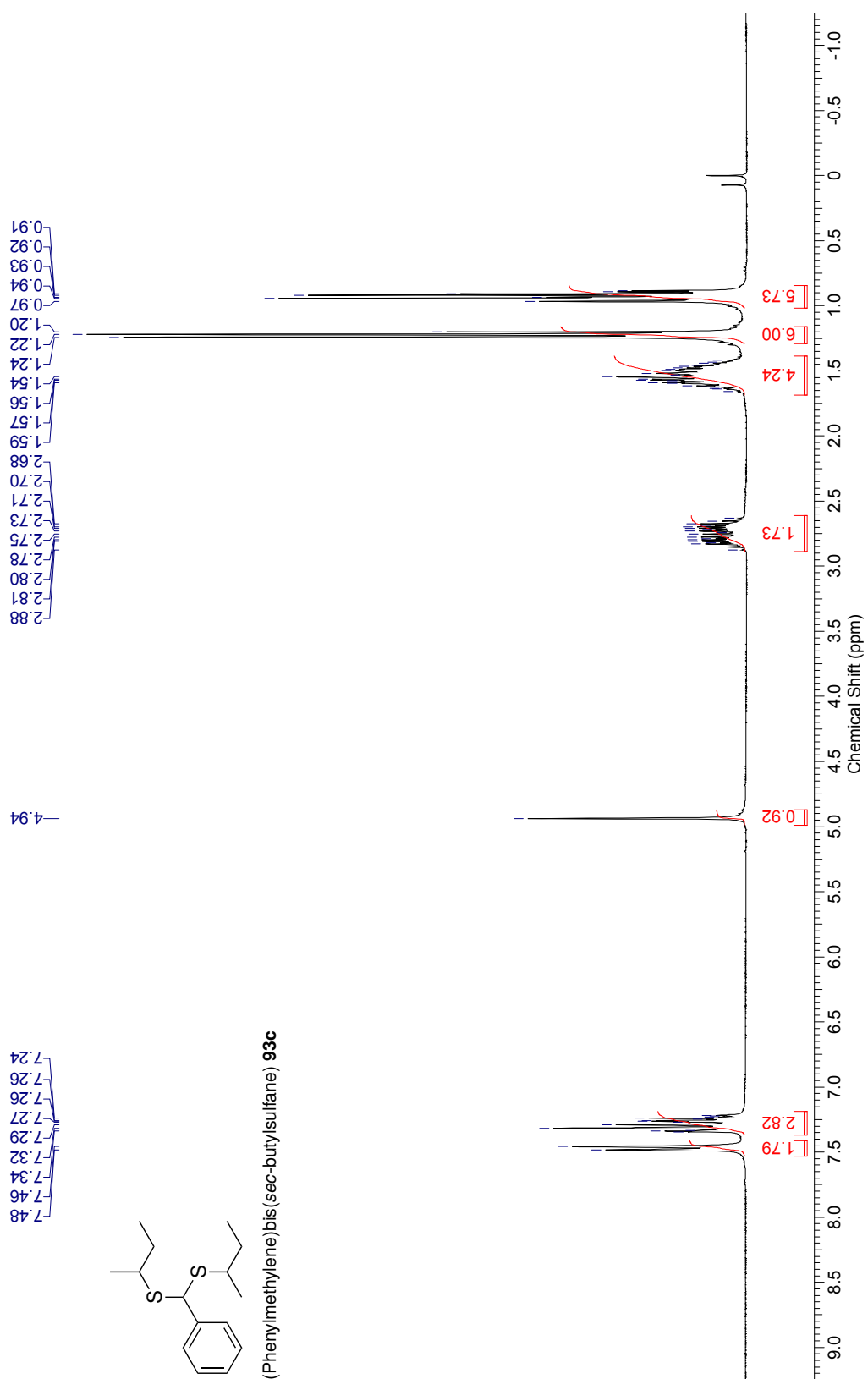
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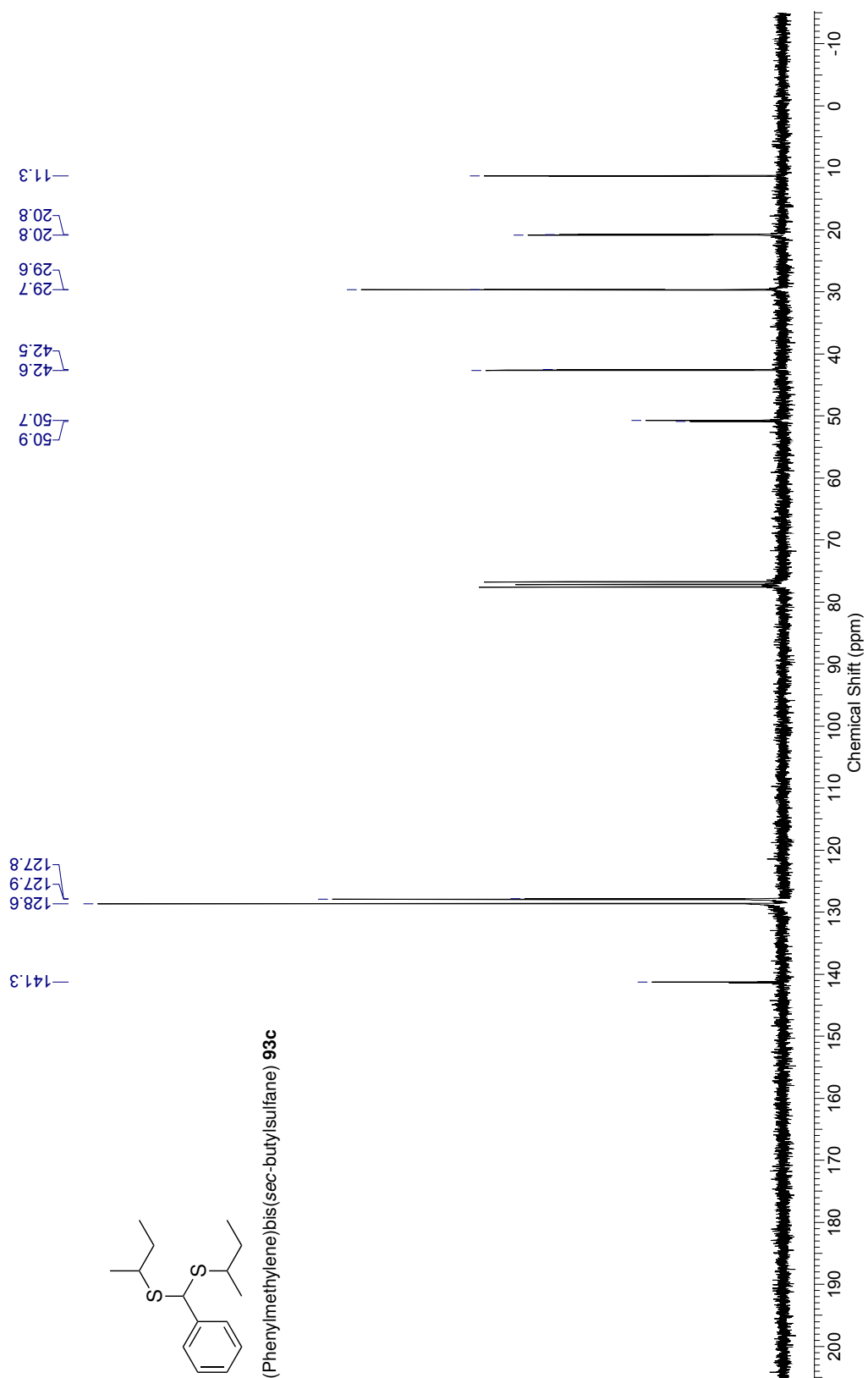
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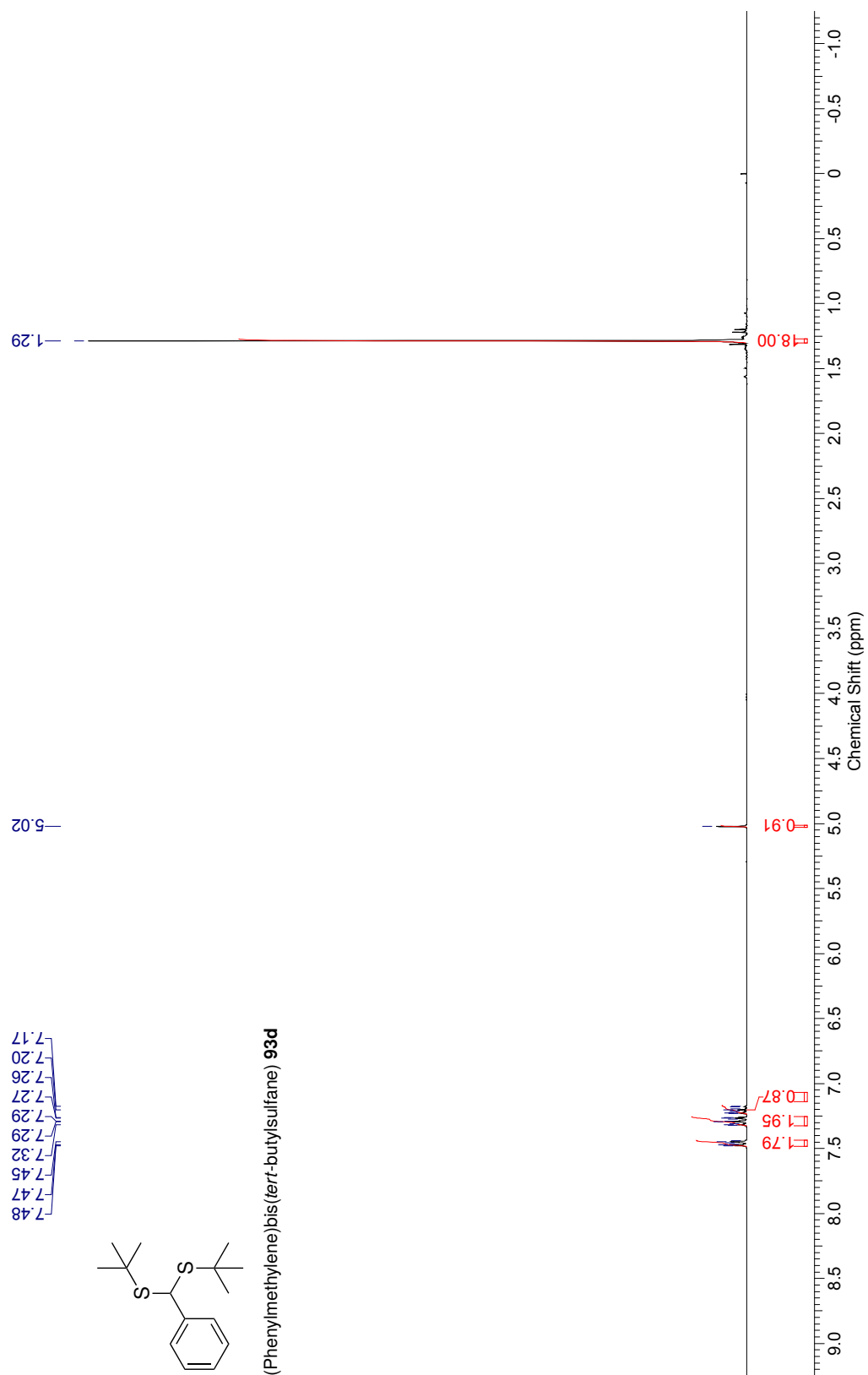
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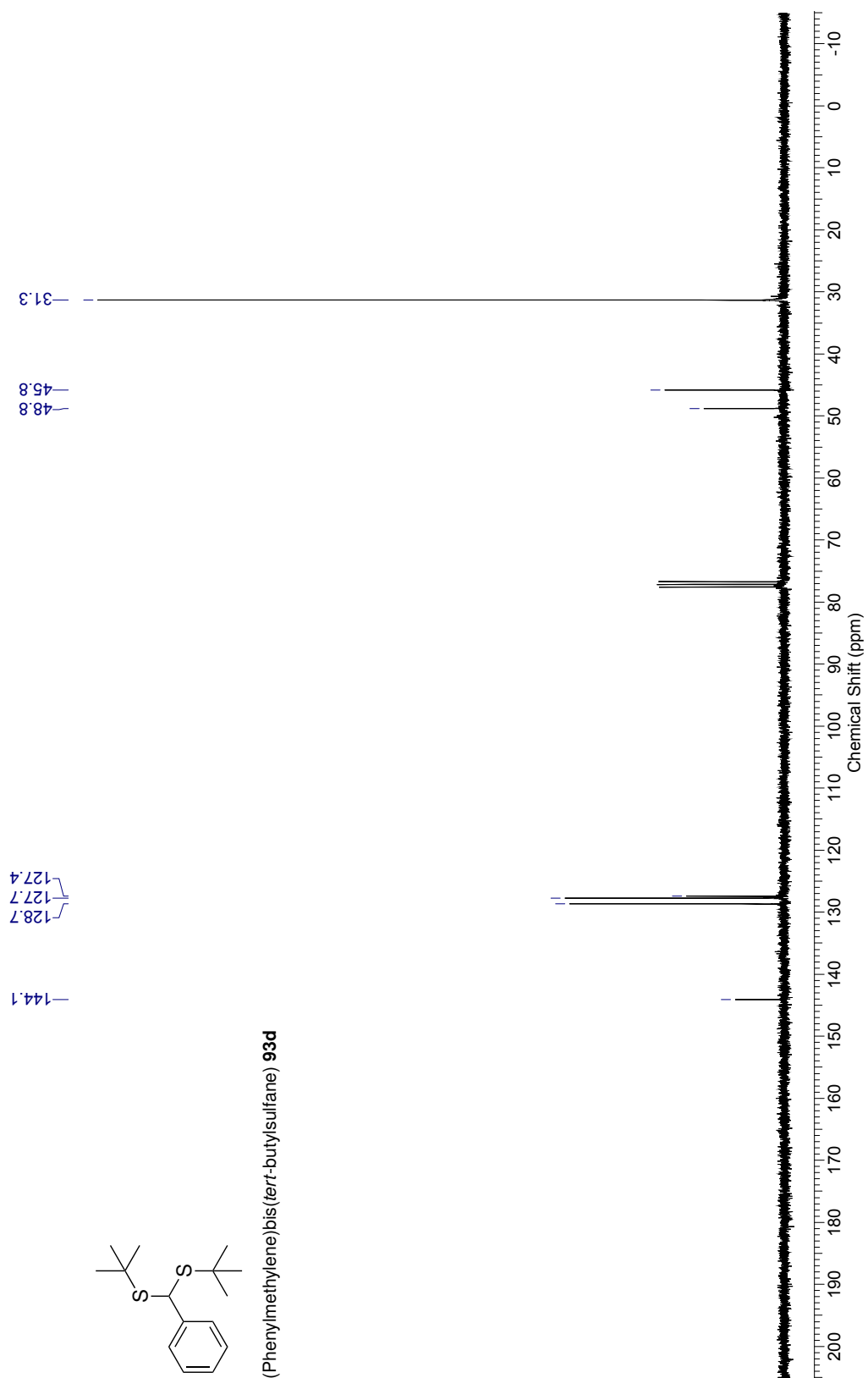
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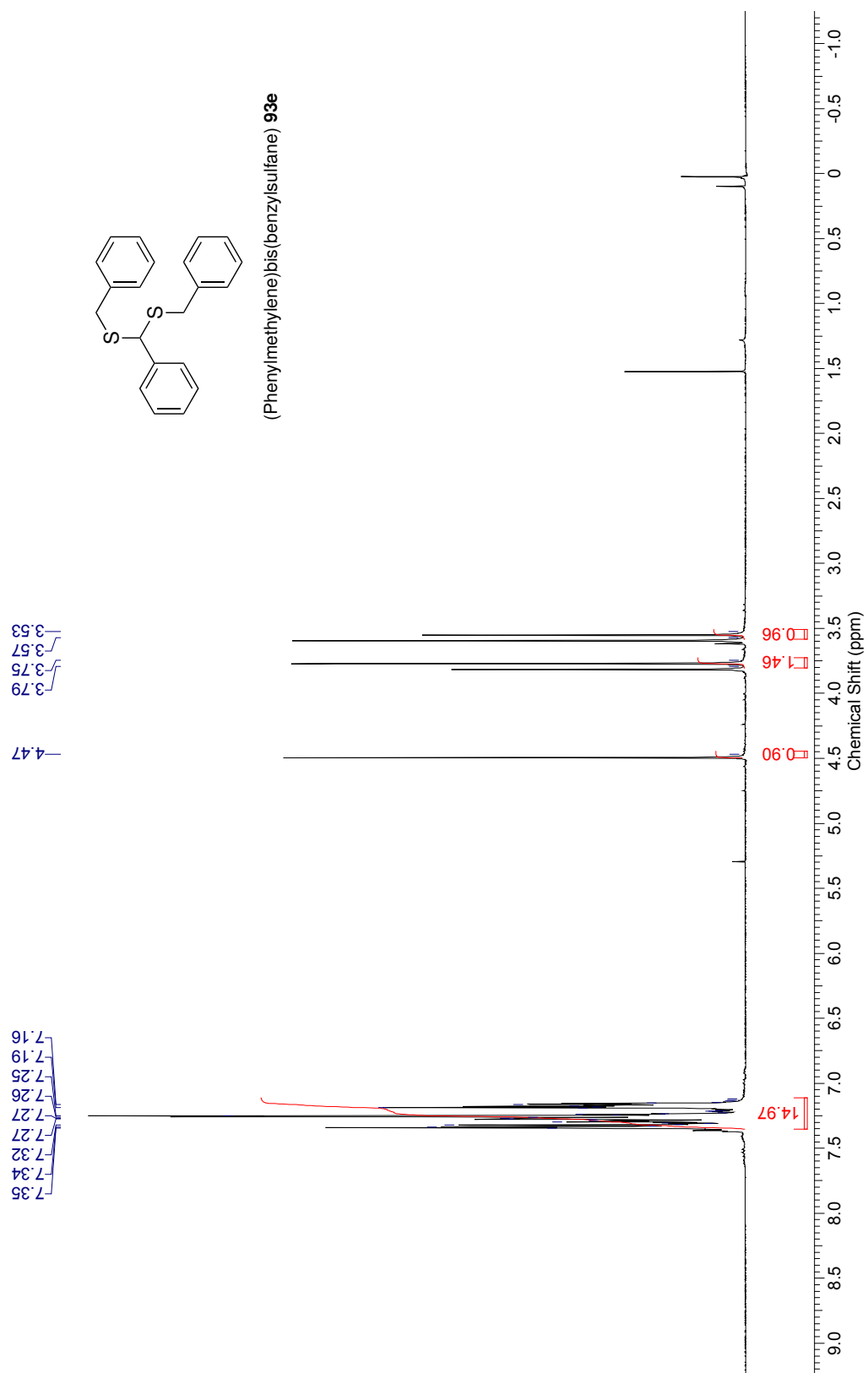
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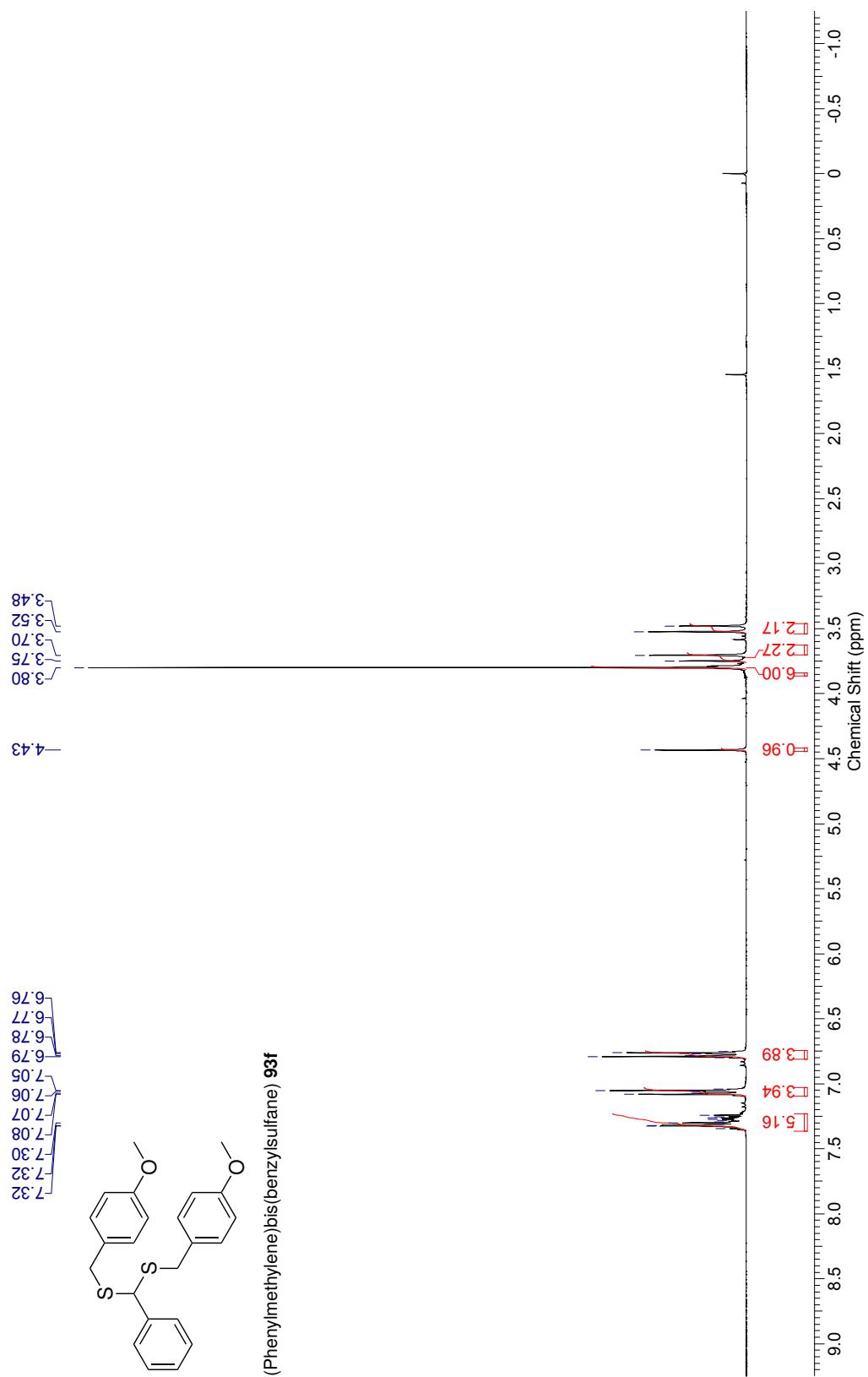
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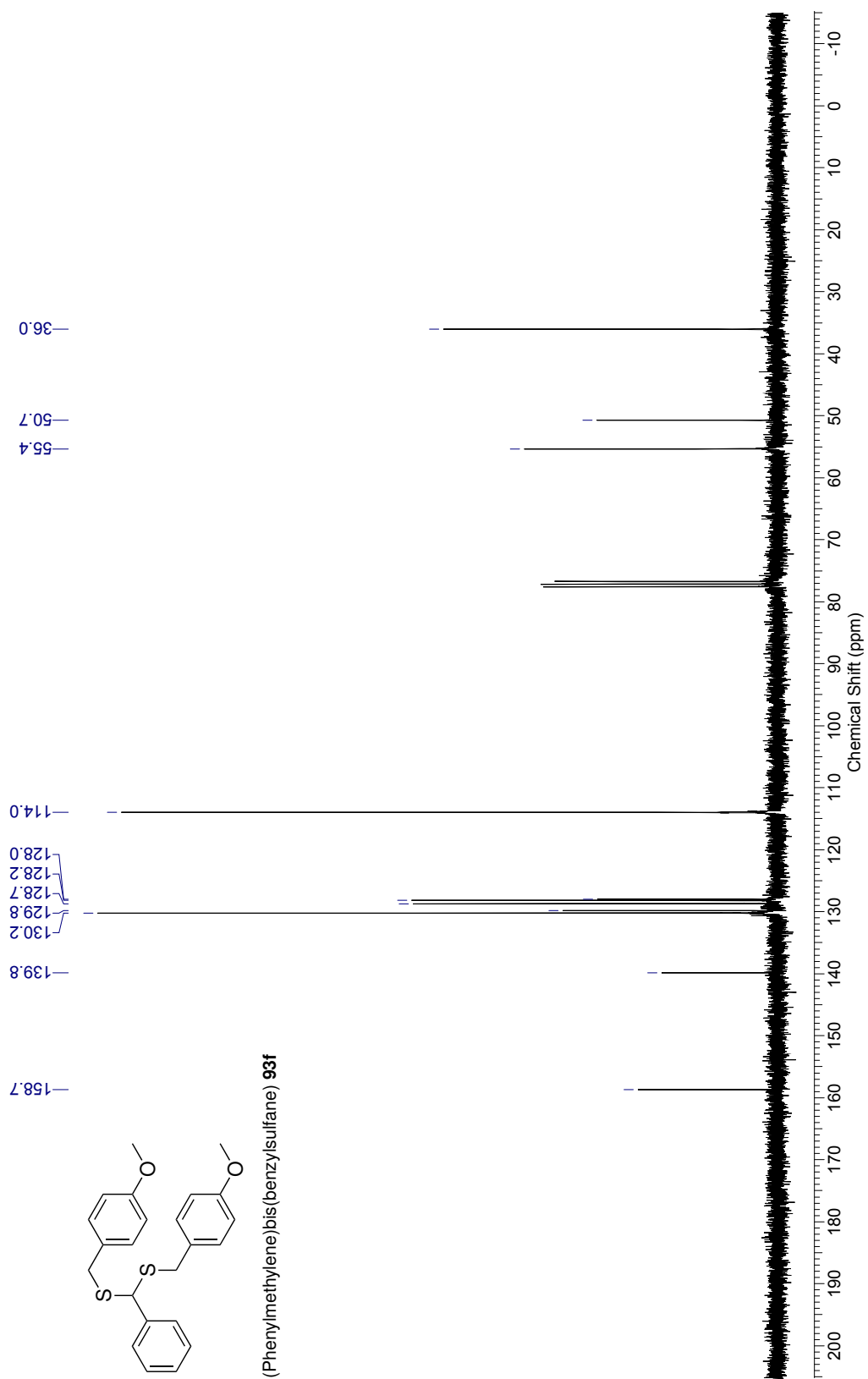
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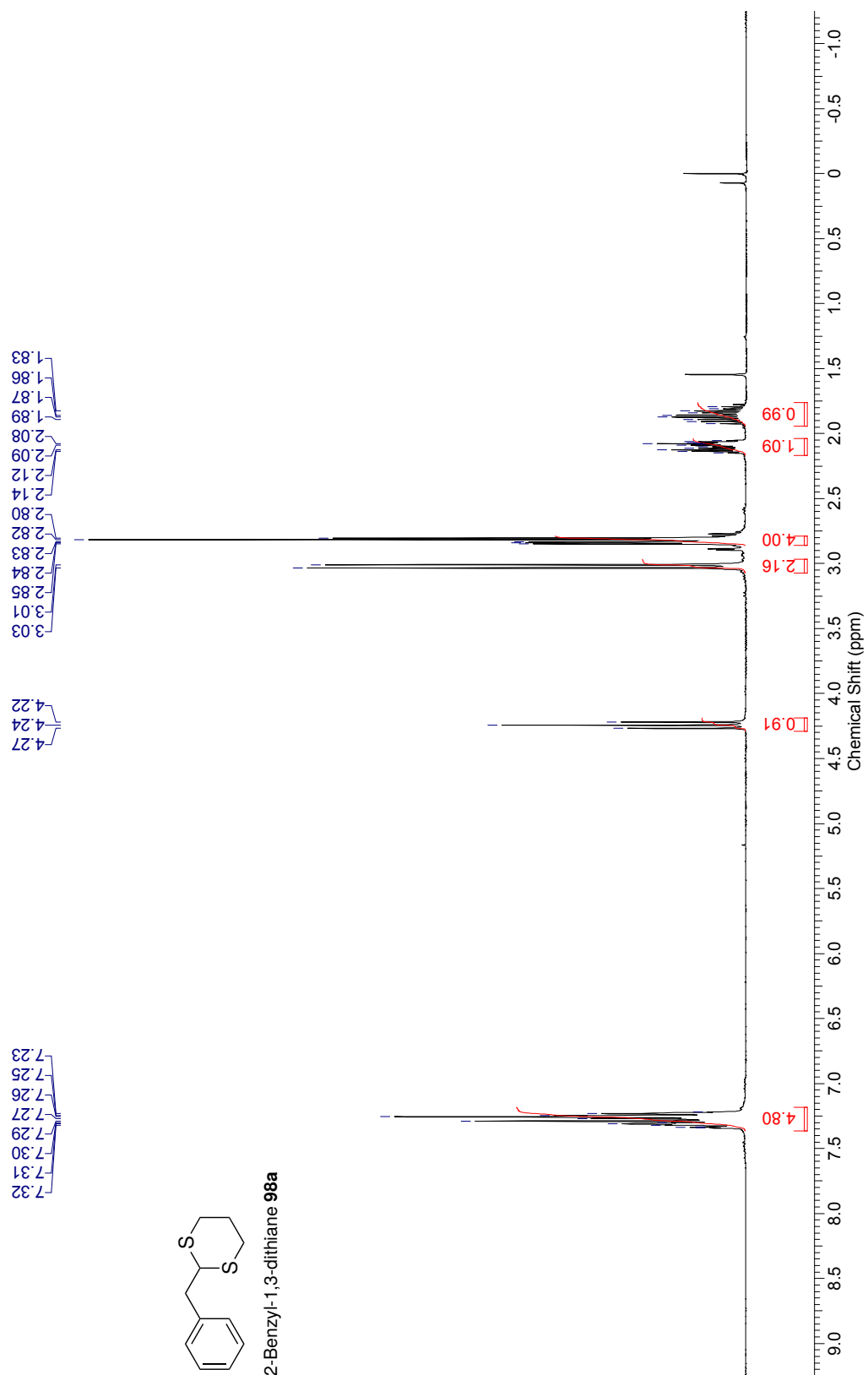
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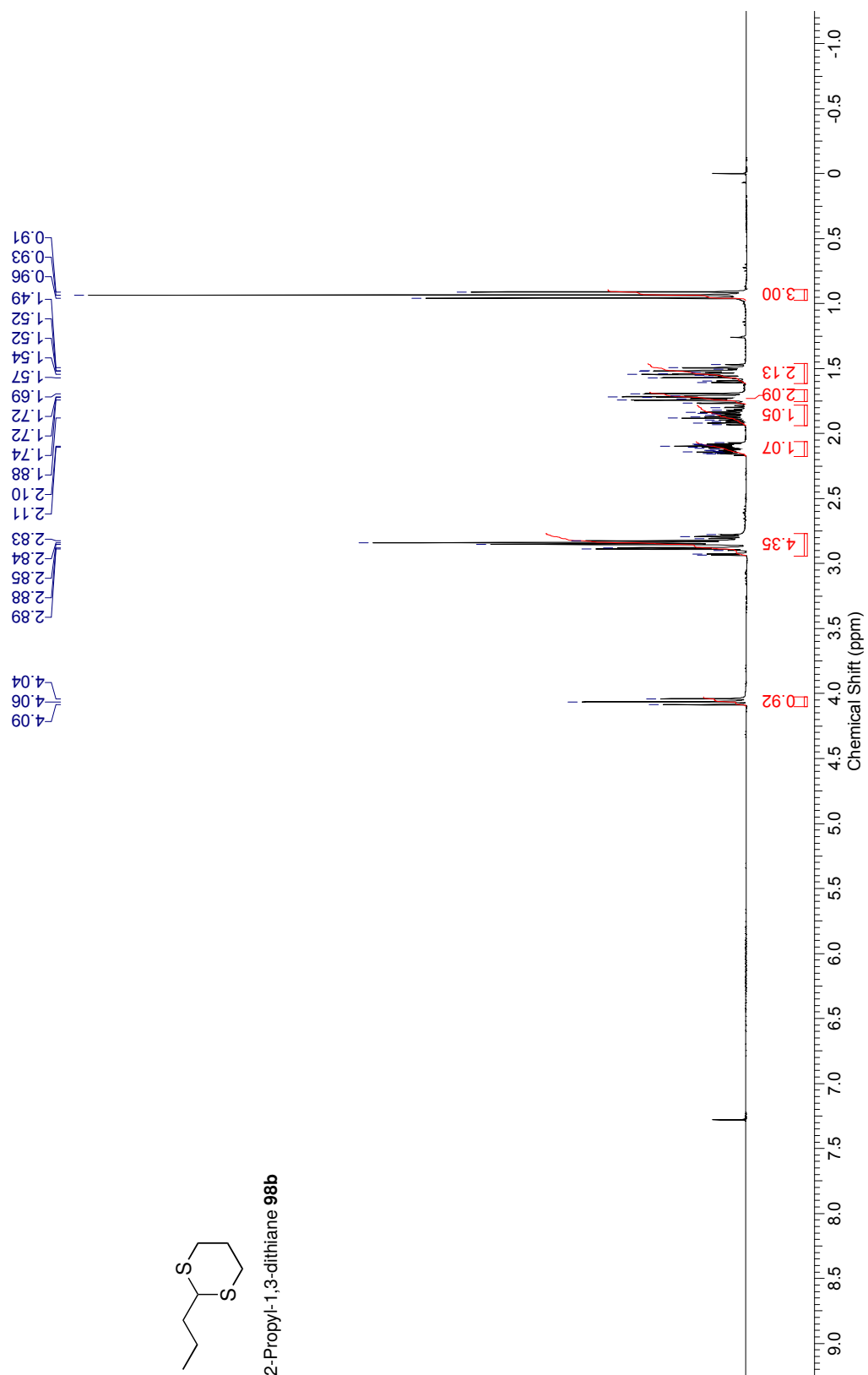
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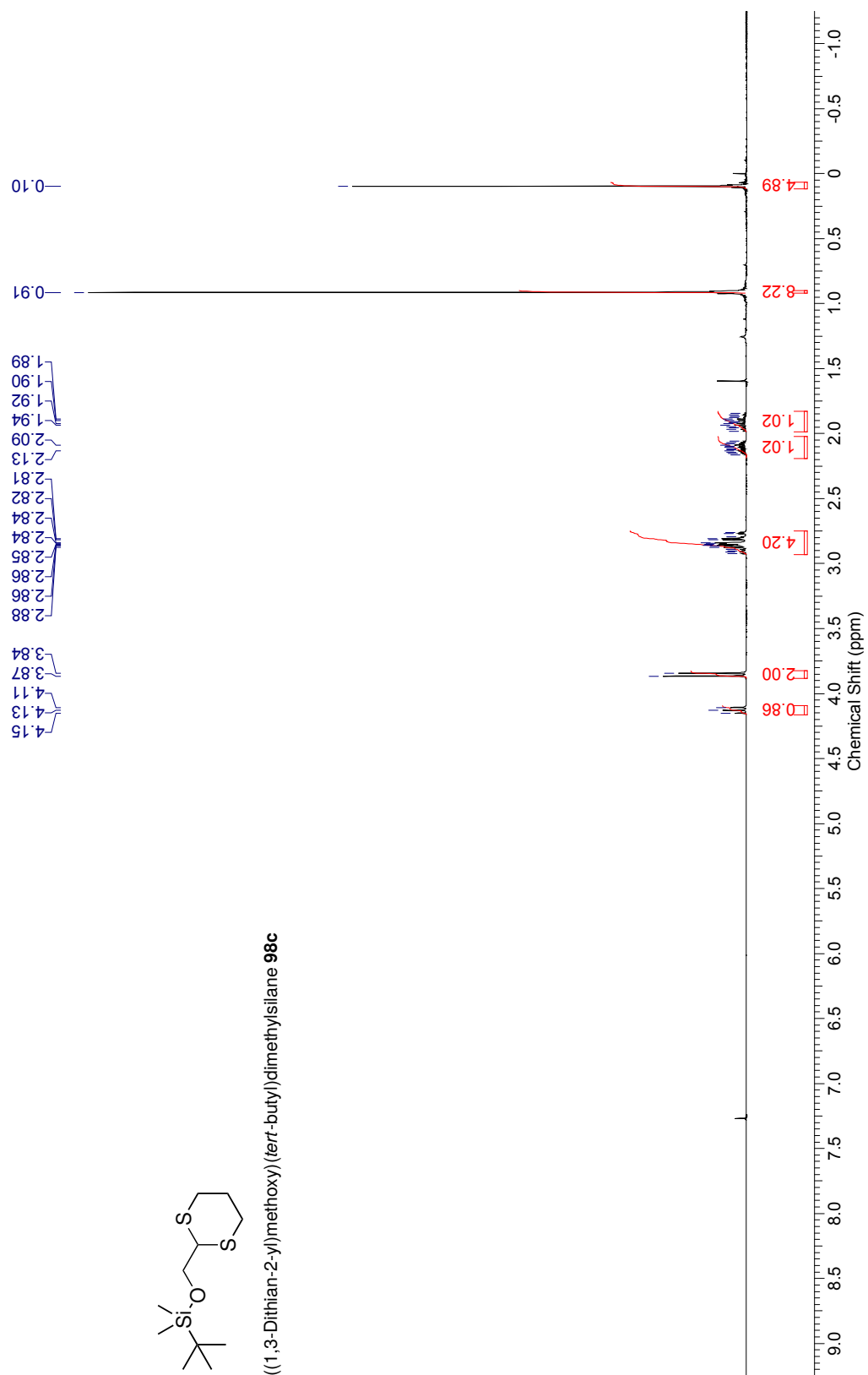
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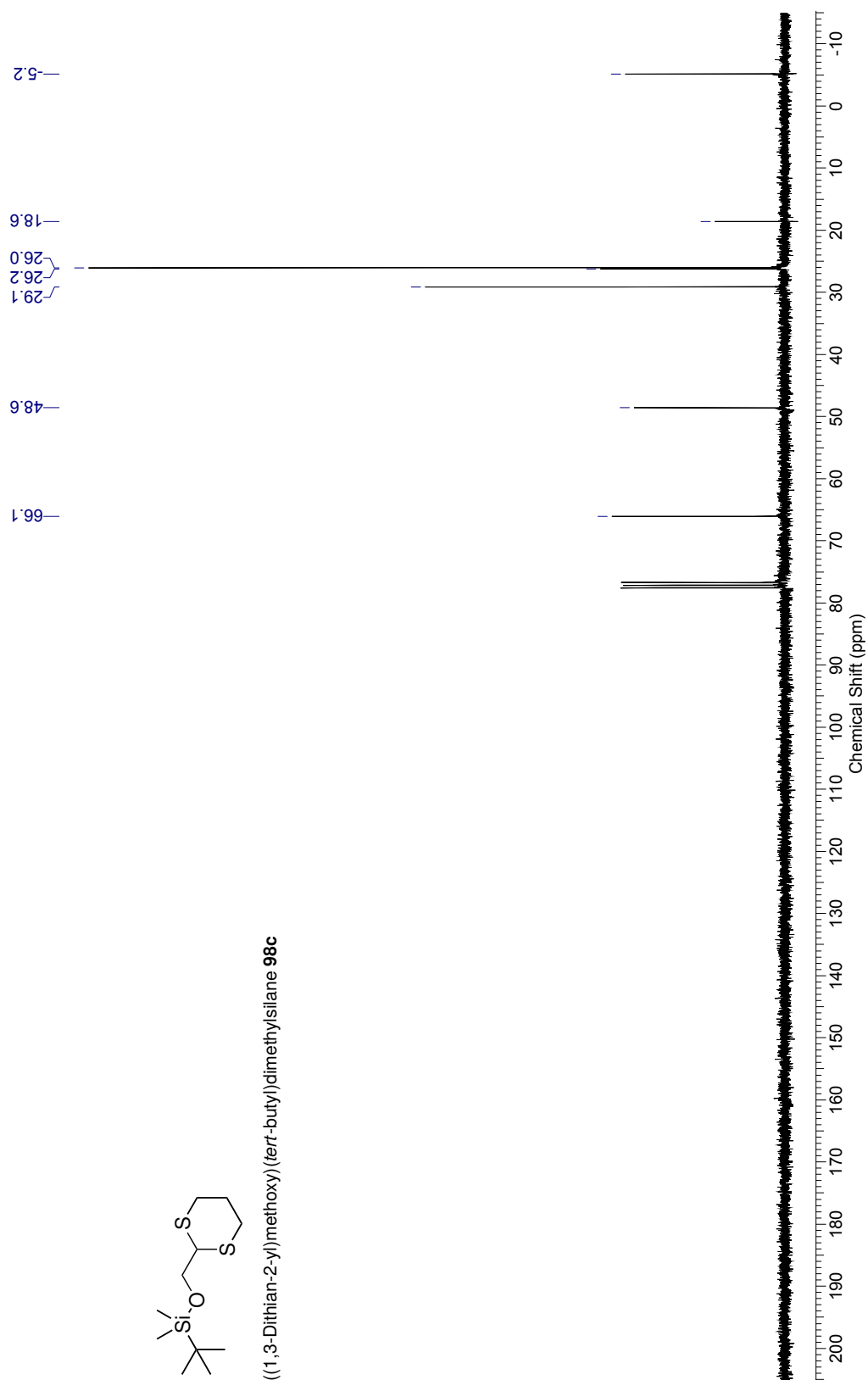
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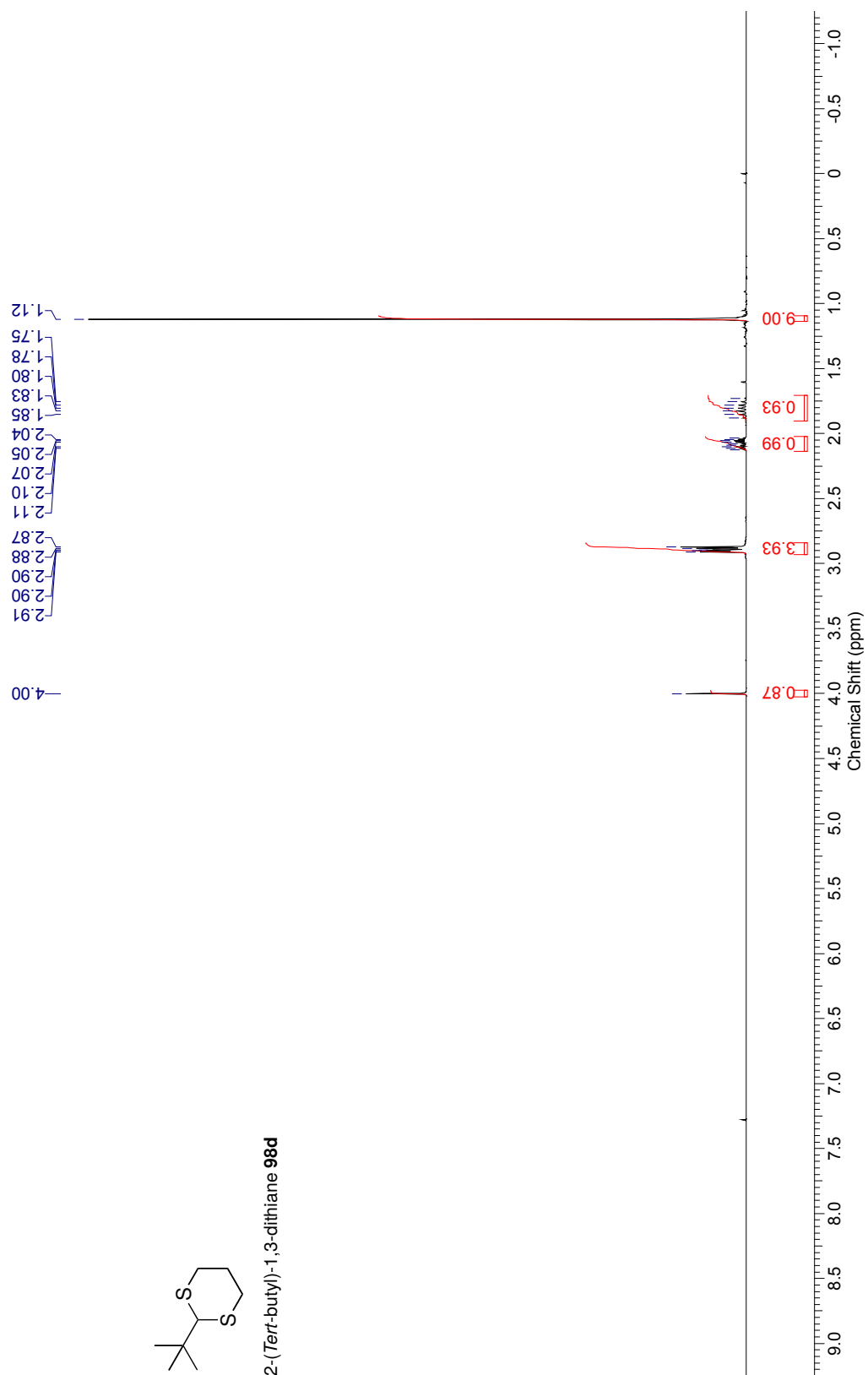
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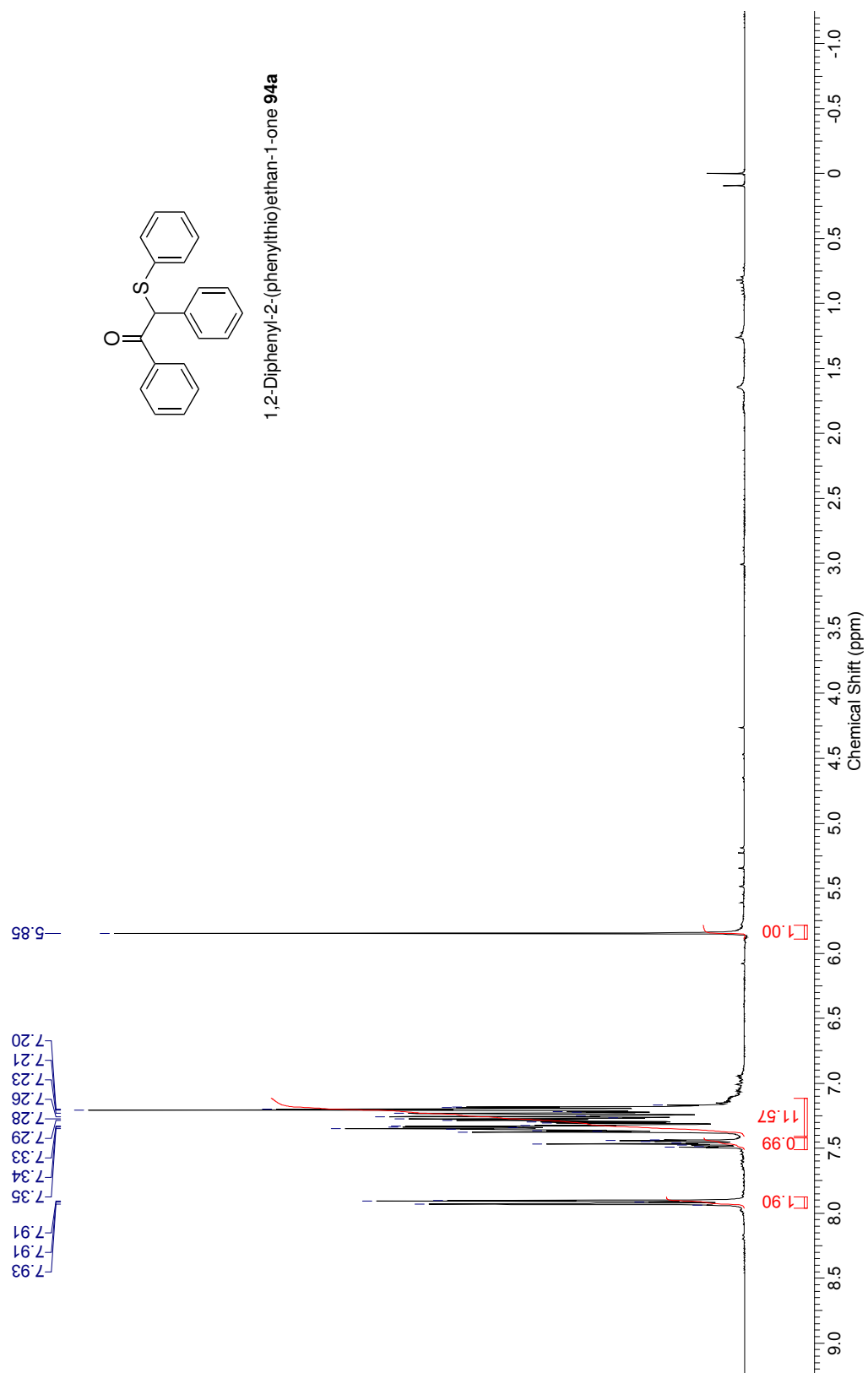
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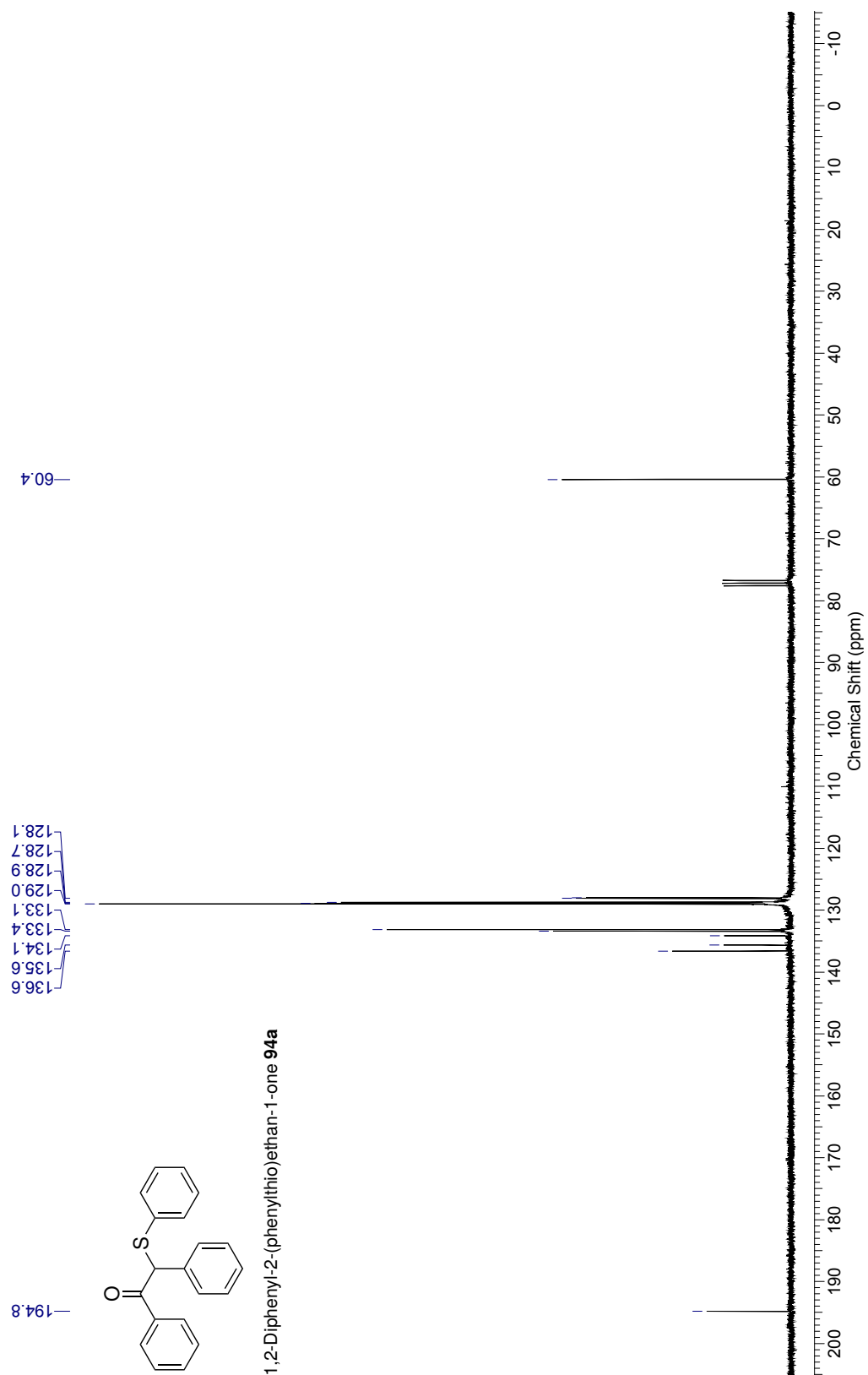
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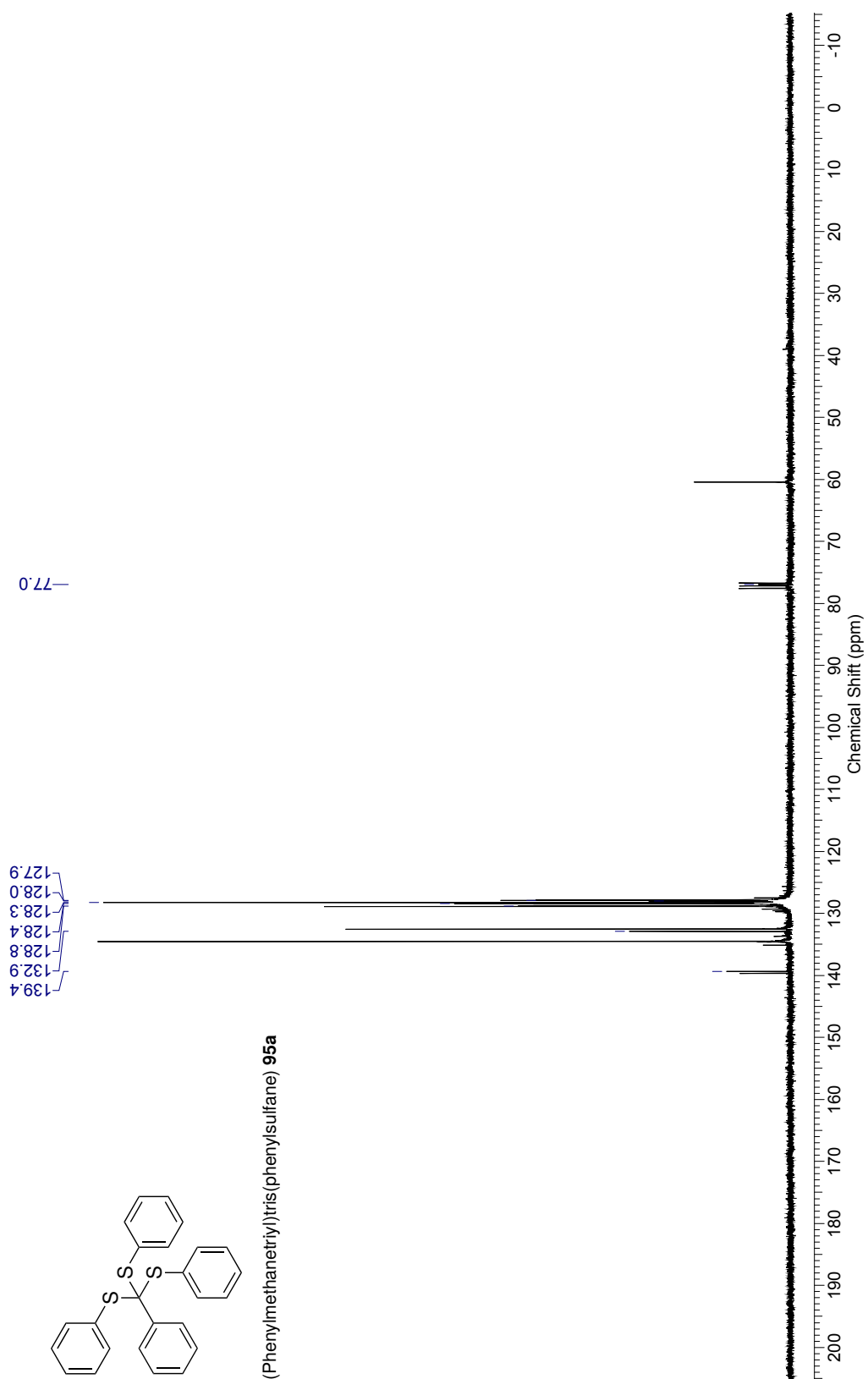
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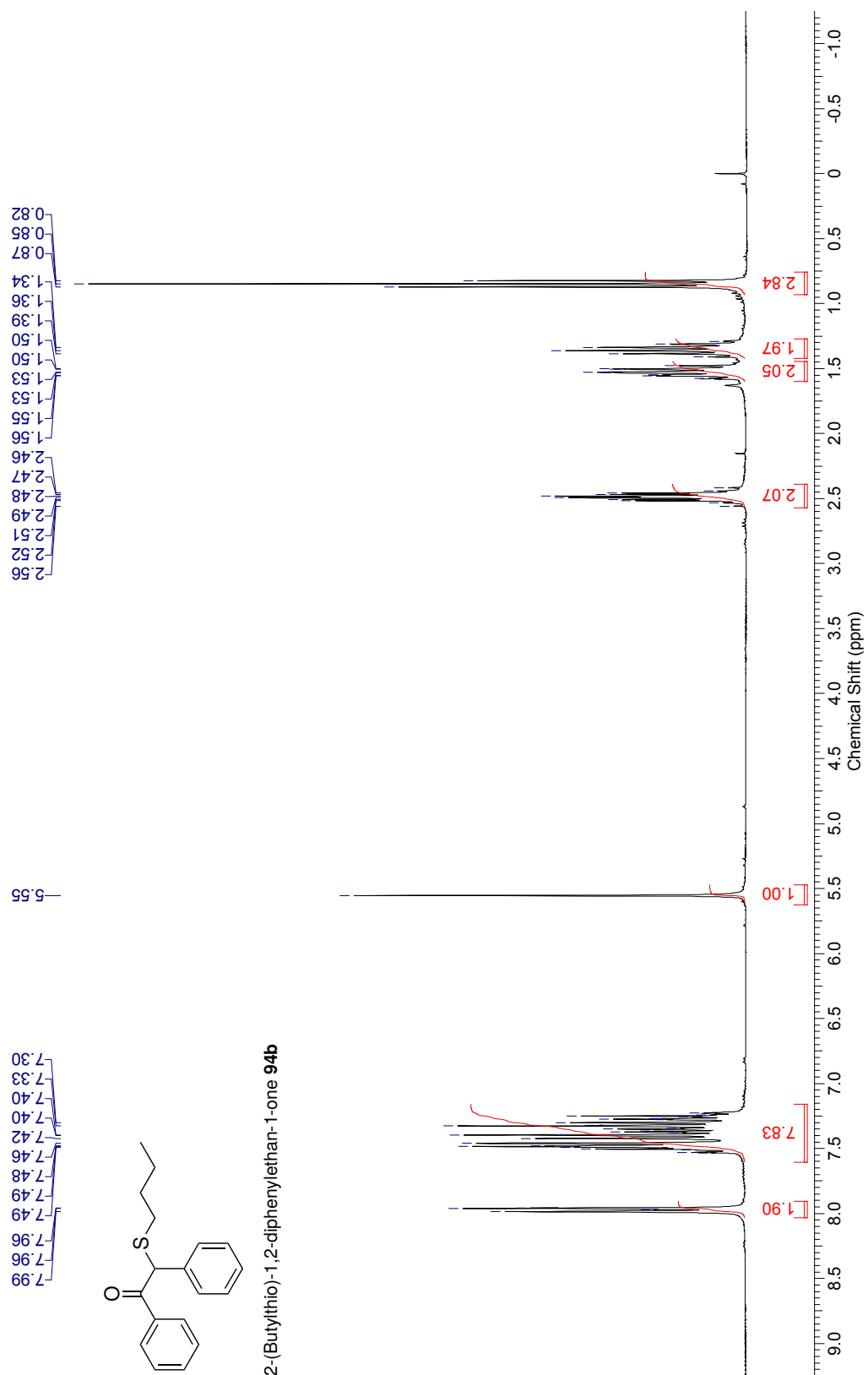
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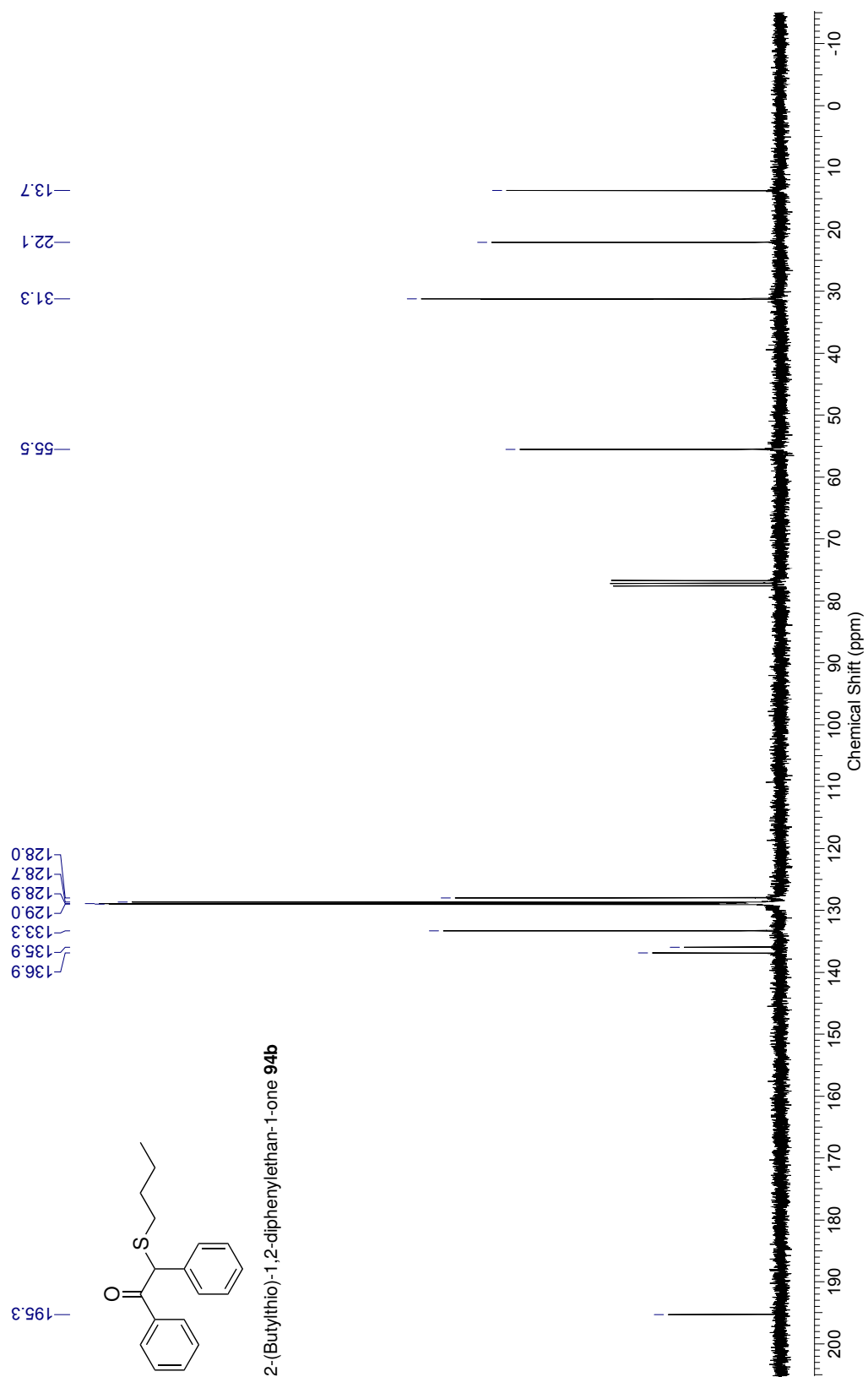
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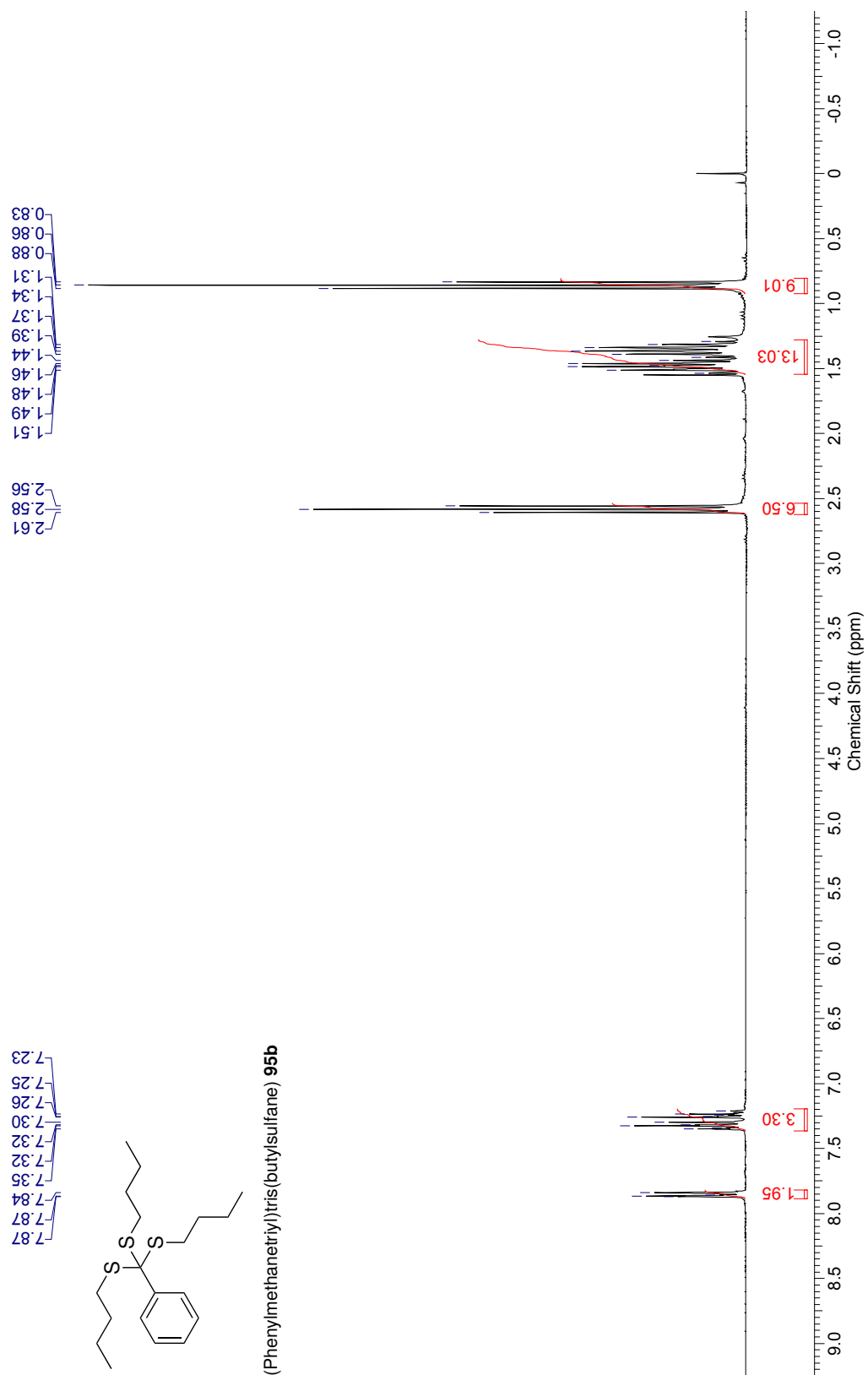
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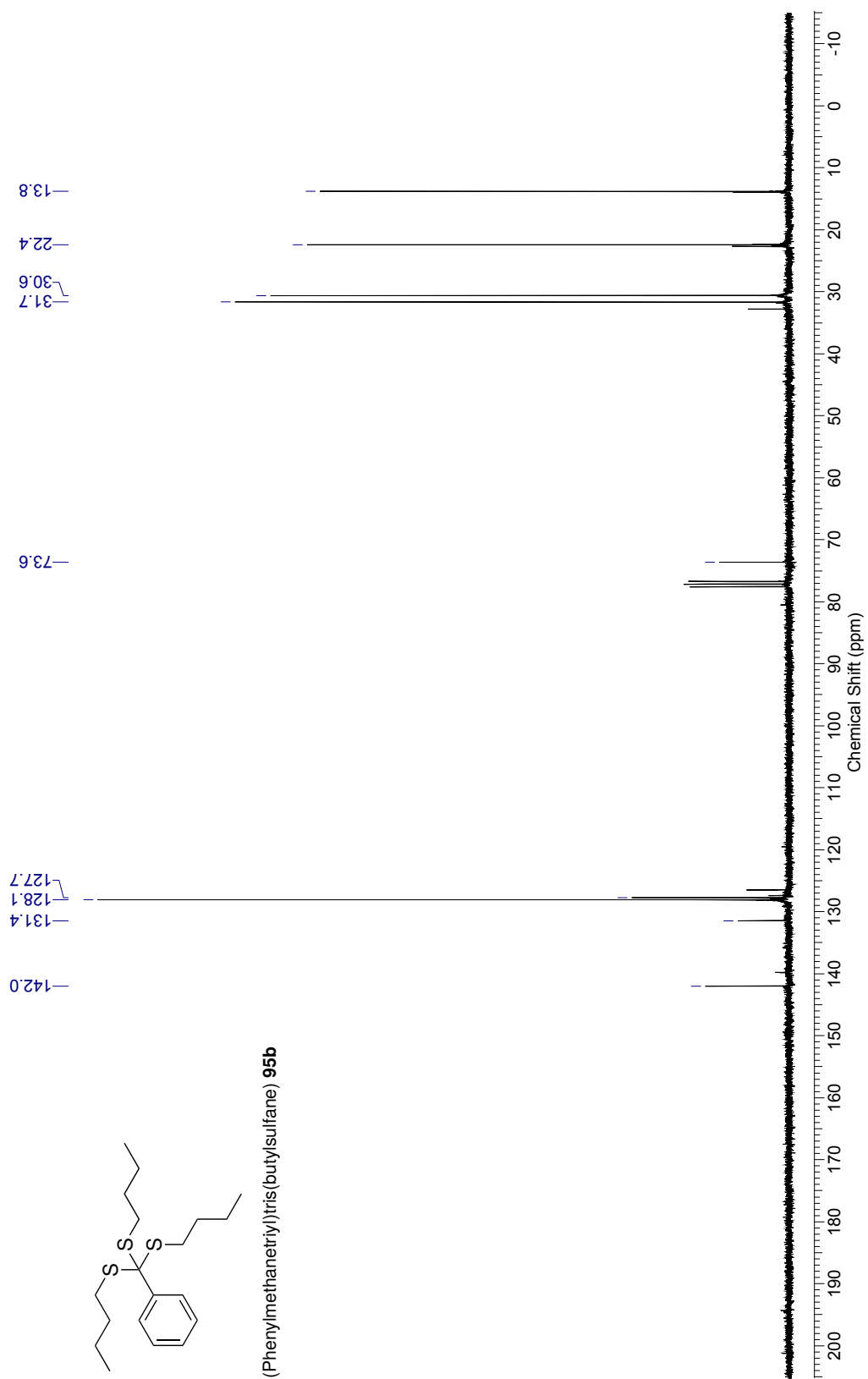
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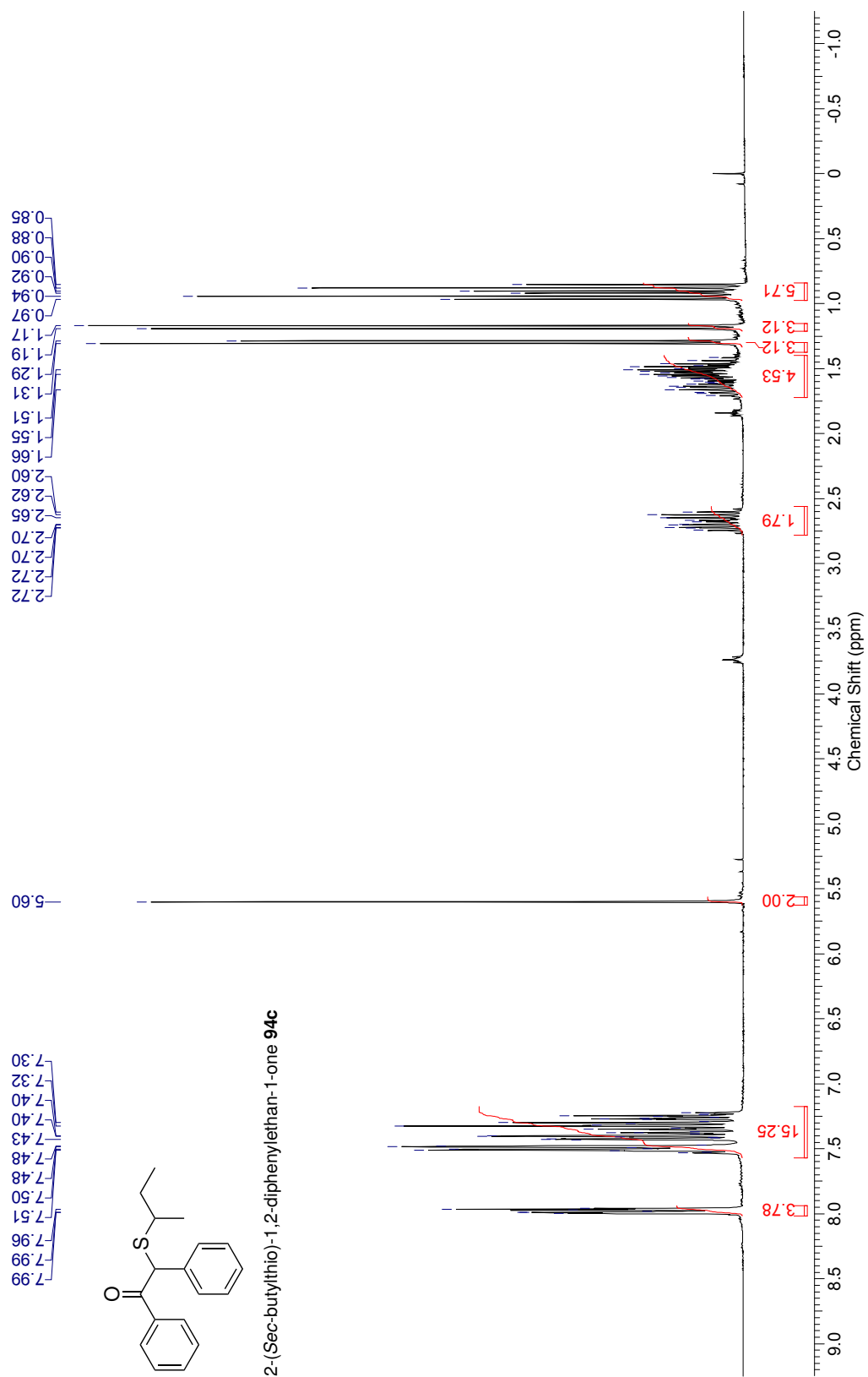
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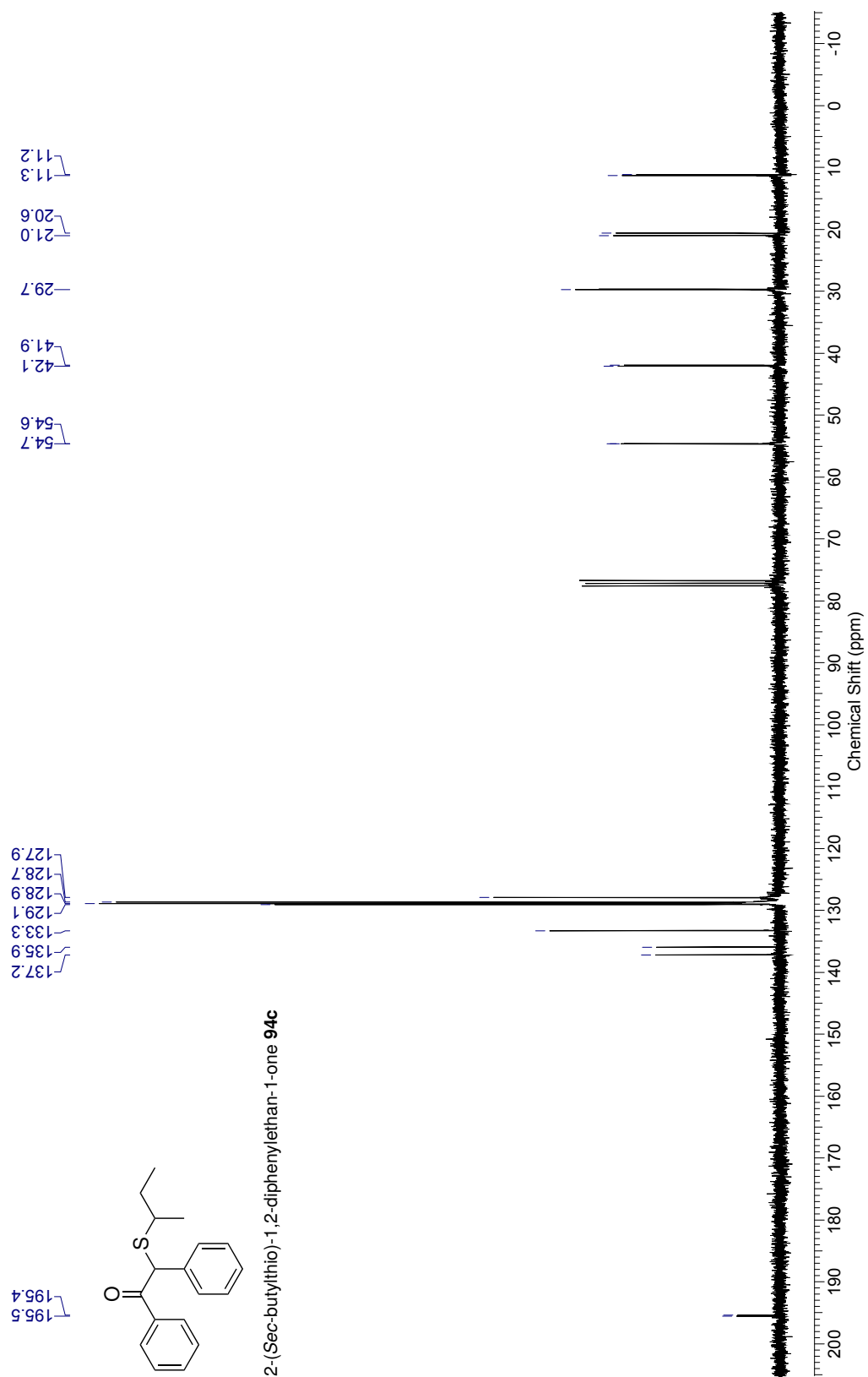
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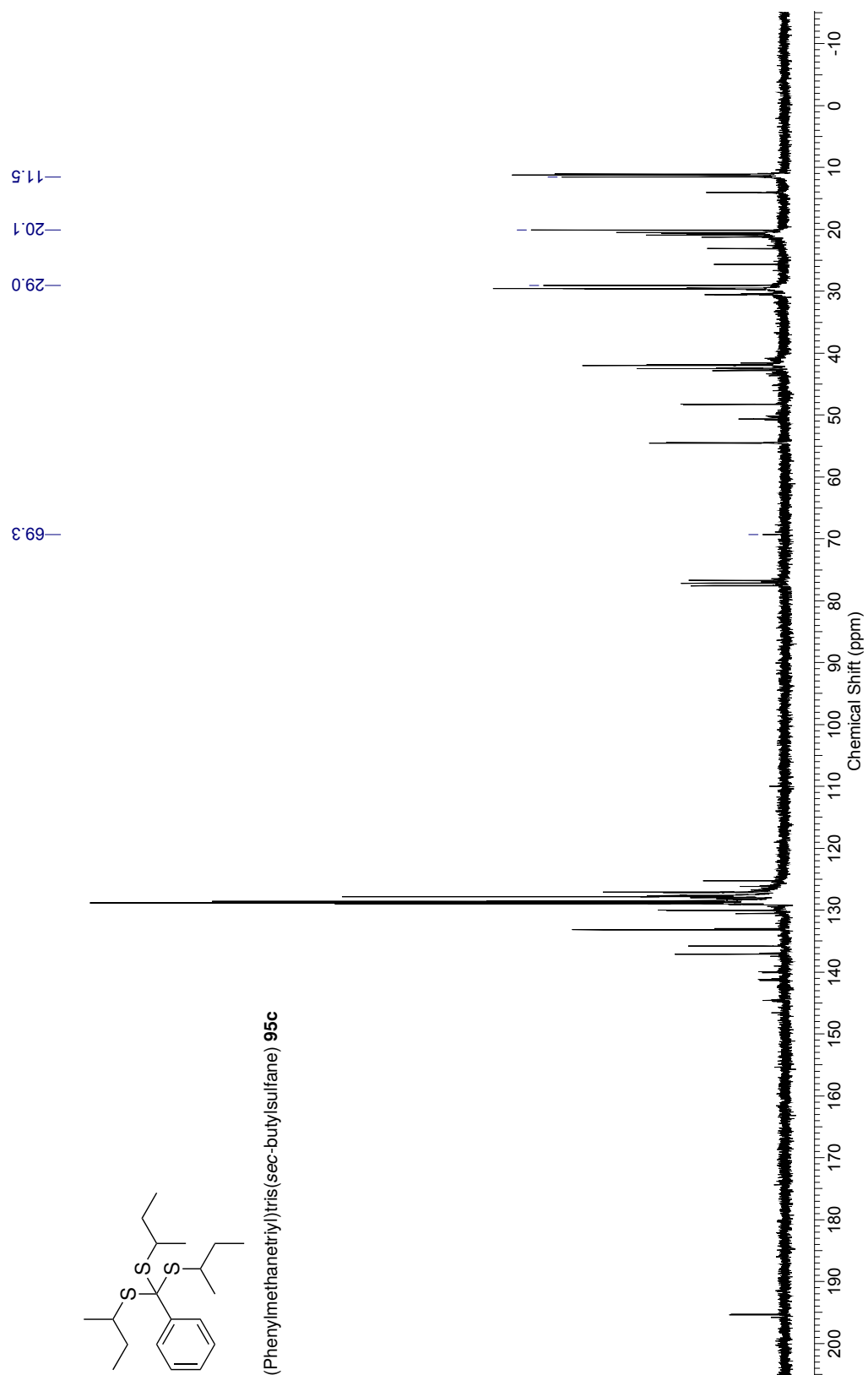
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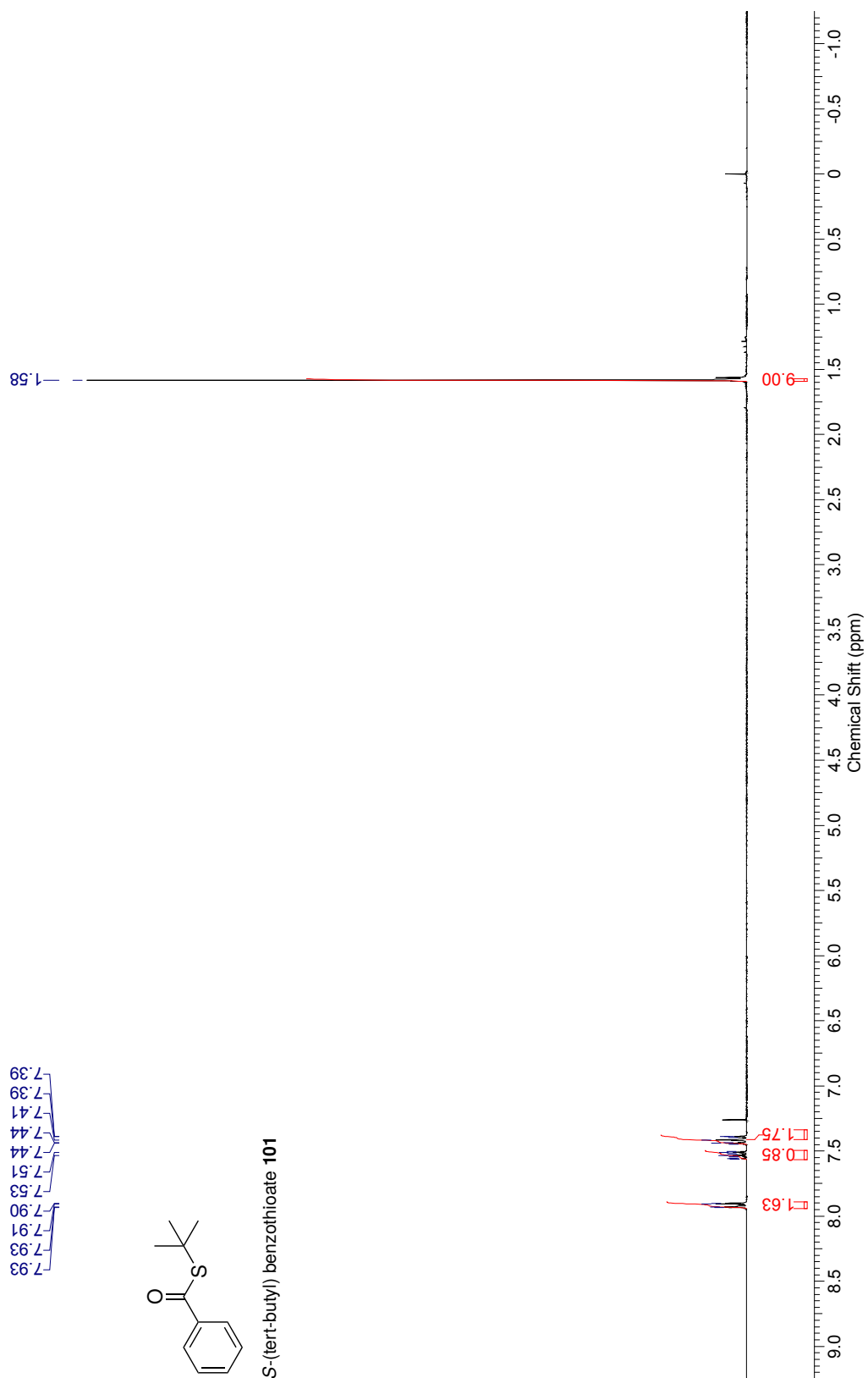
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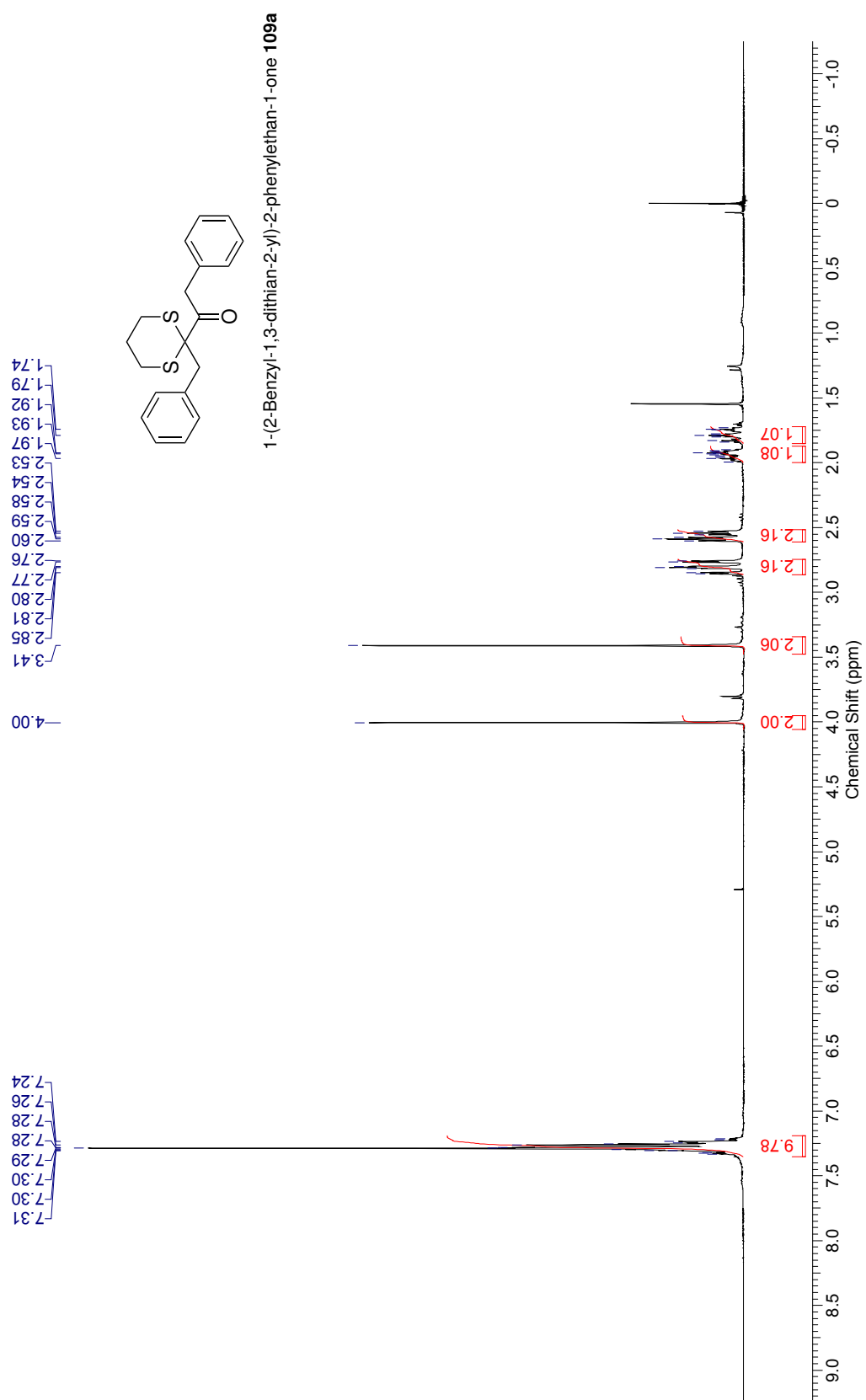
Appendix 22. ^{13}C NMR of compound 95b

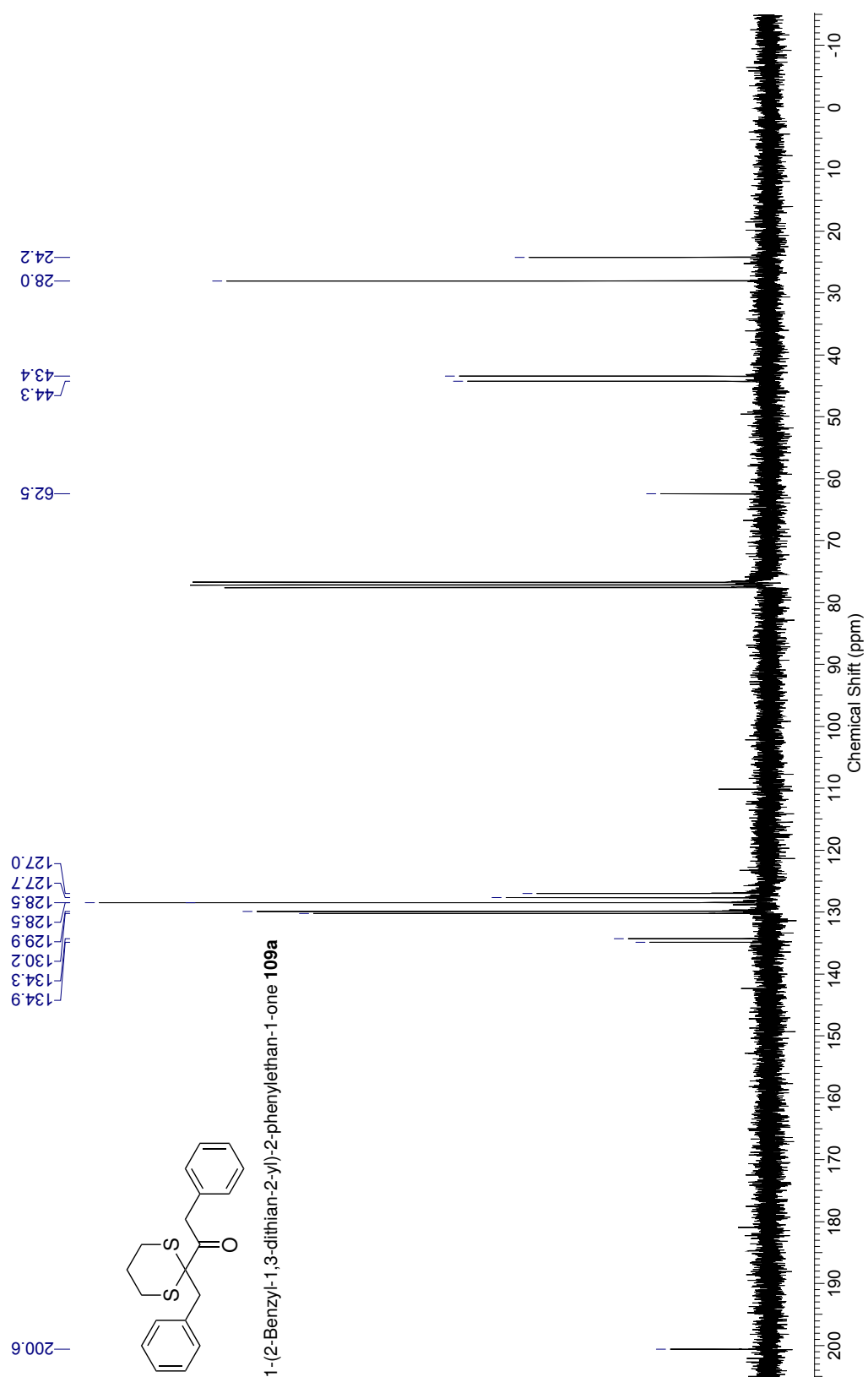
Appendix 23. ^1H NMR of compound 94c

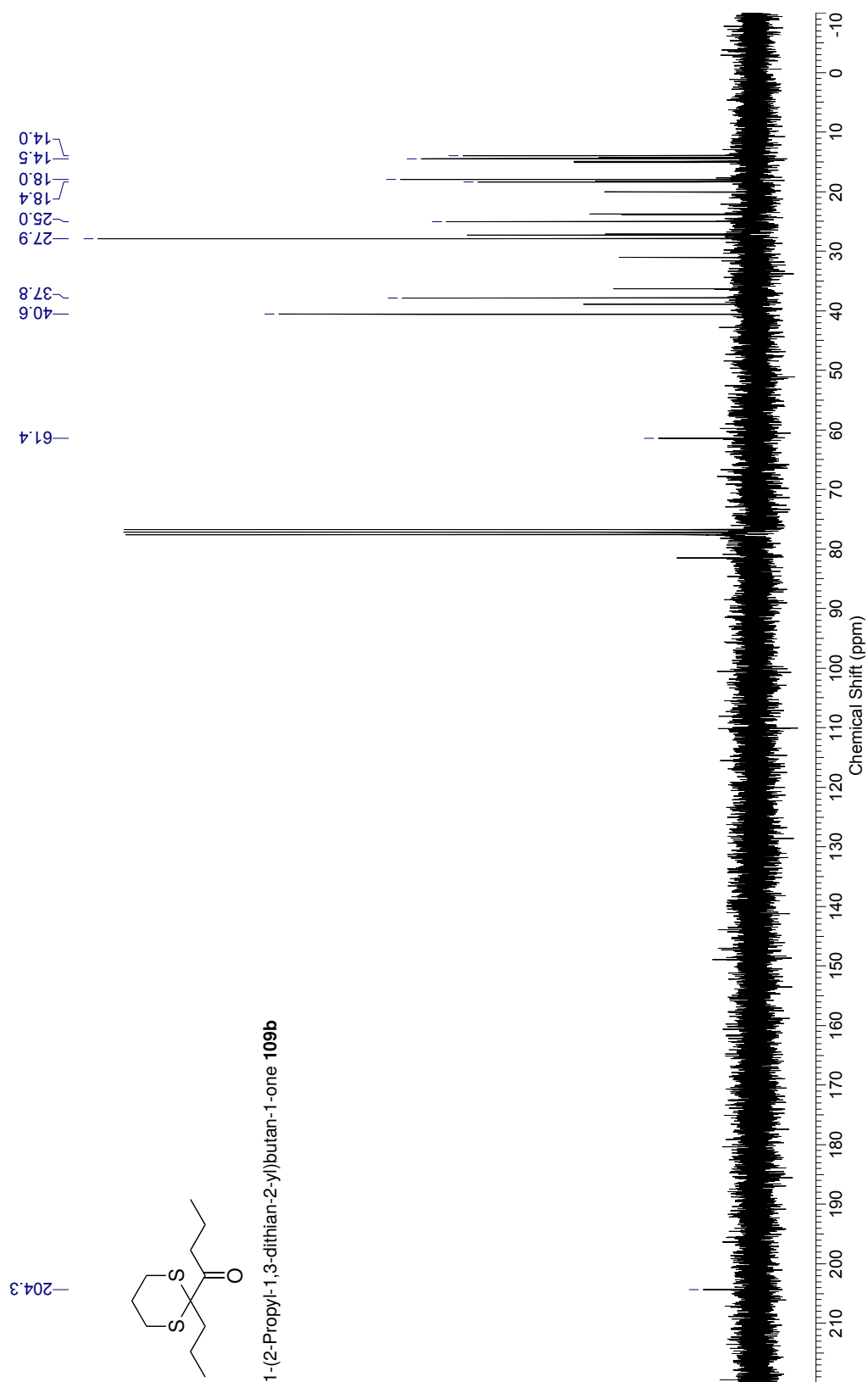
Appendix 24. ^{13}C NMR of compound 94c

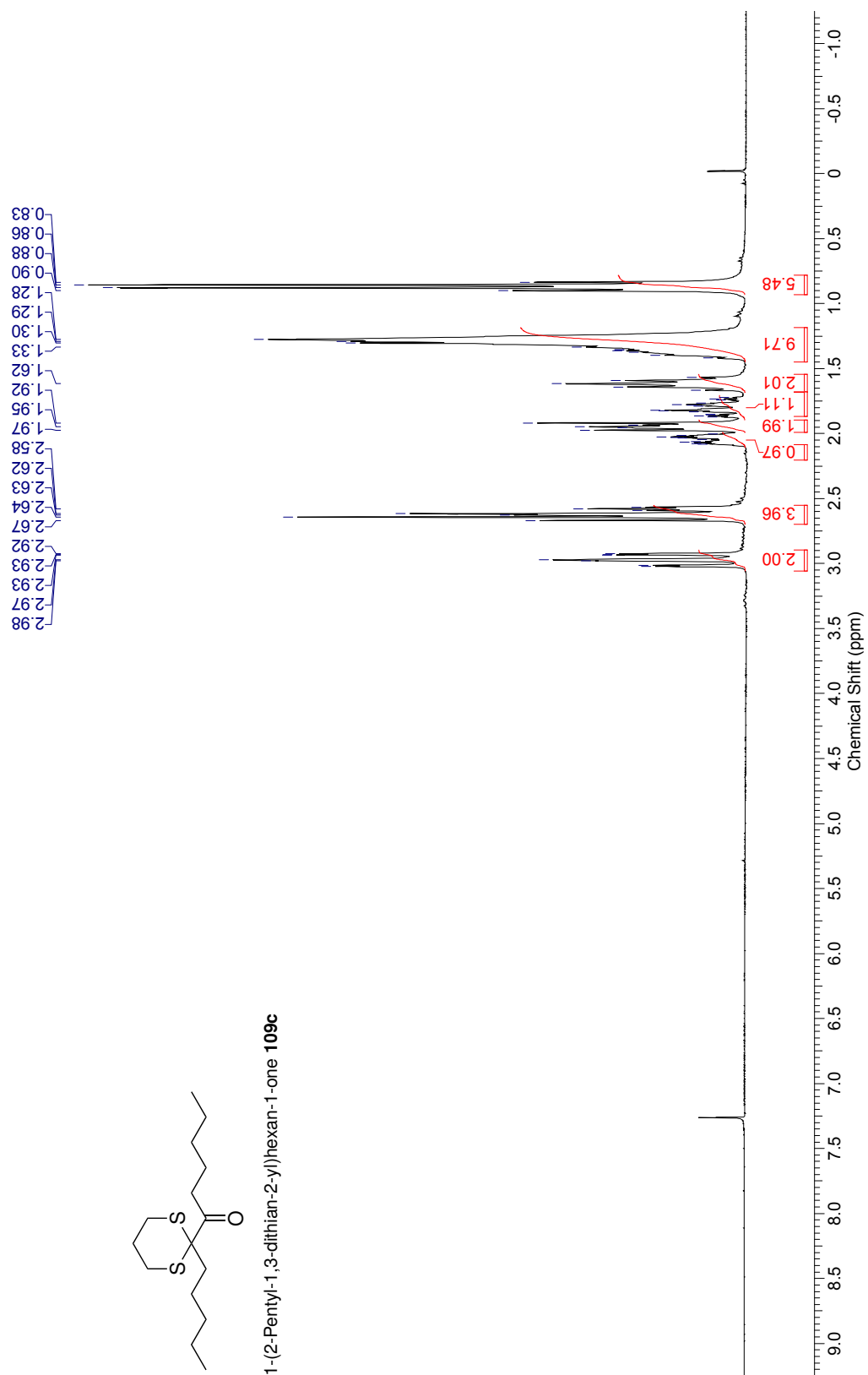
Appendix 25. ^{13}C NMR of compound 95c

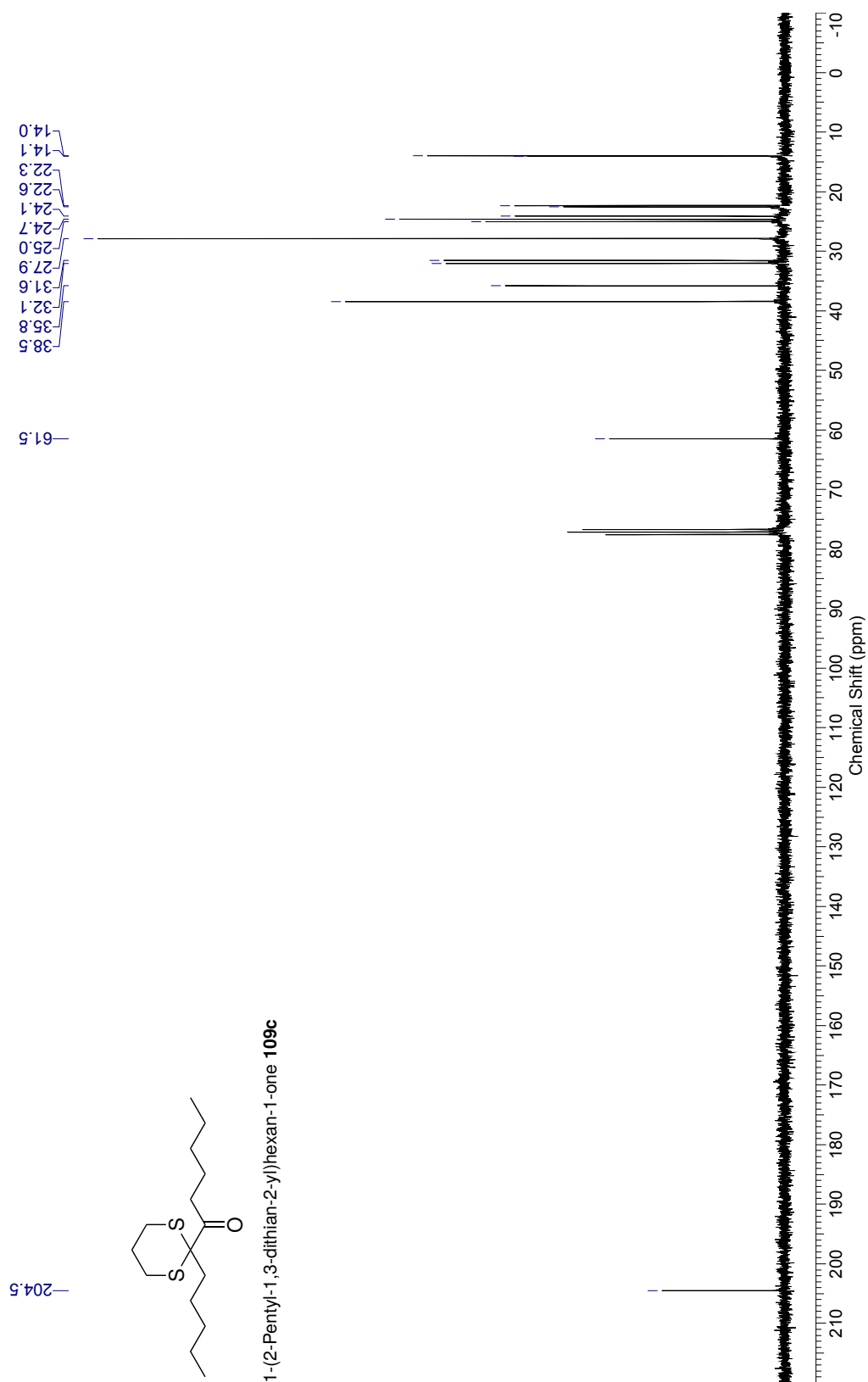
Appendix 26. ^1H NMR of compound 101

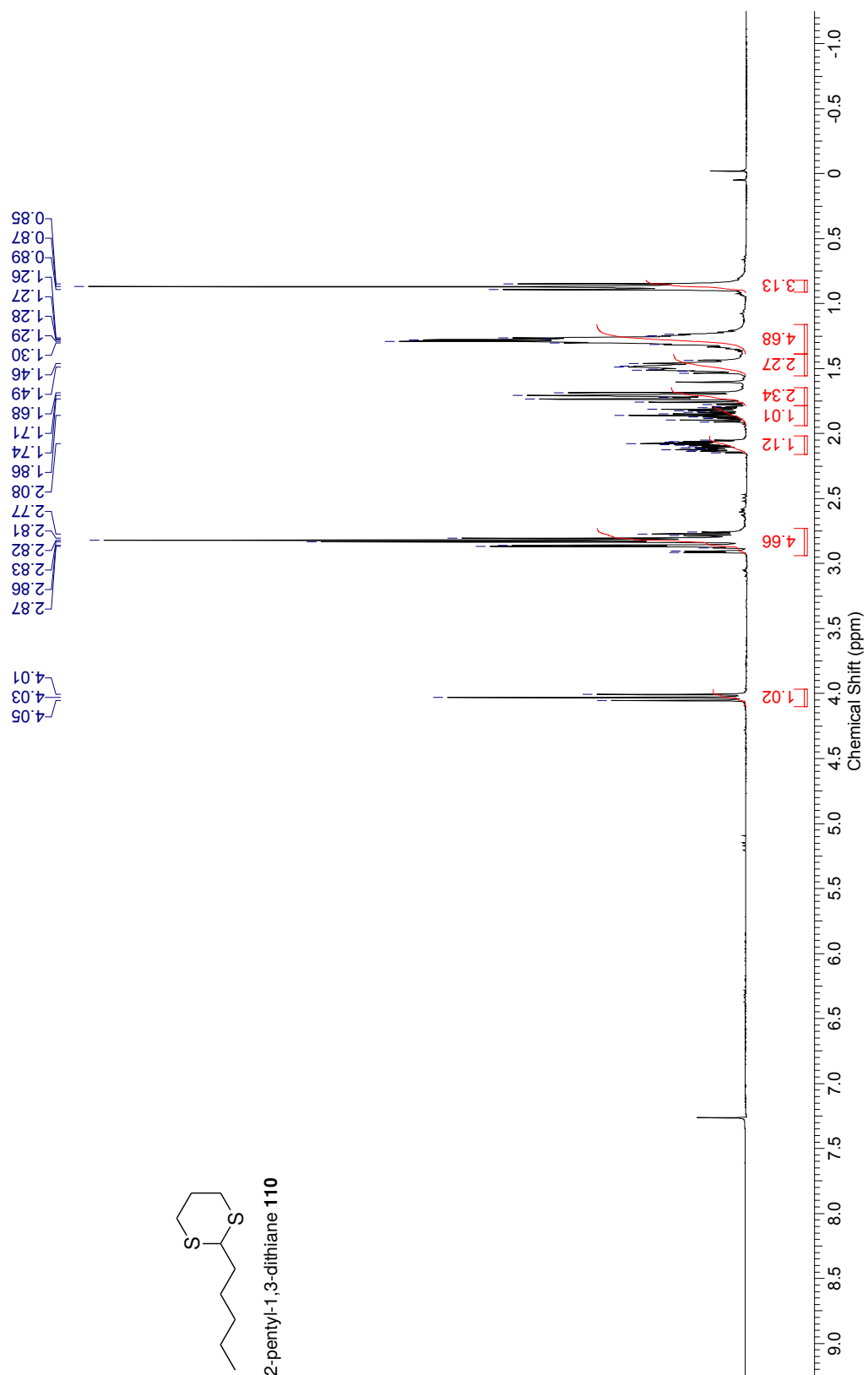
Appendix 27. ^1H NMR of compound 109a

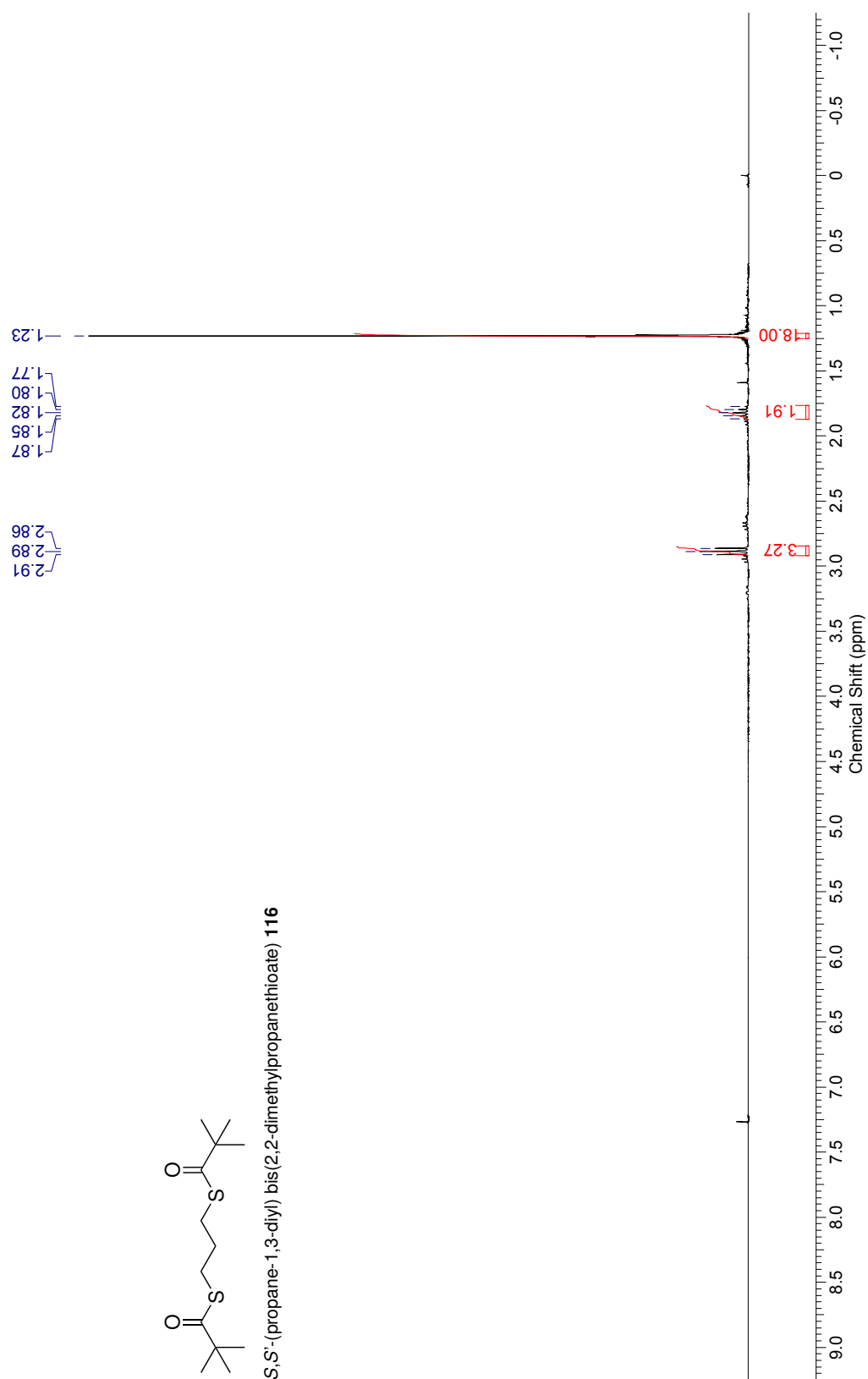
Appendix 28. ^{13}C NMR of compound 109a

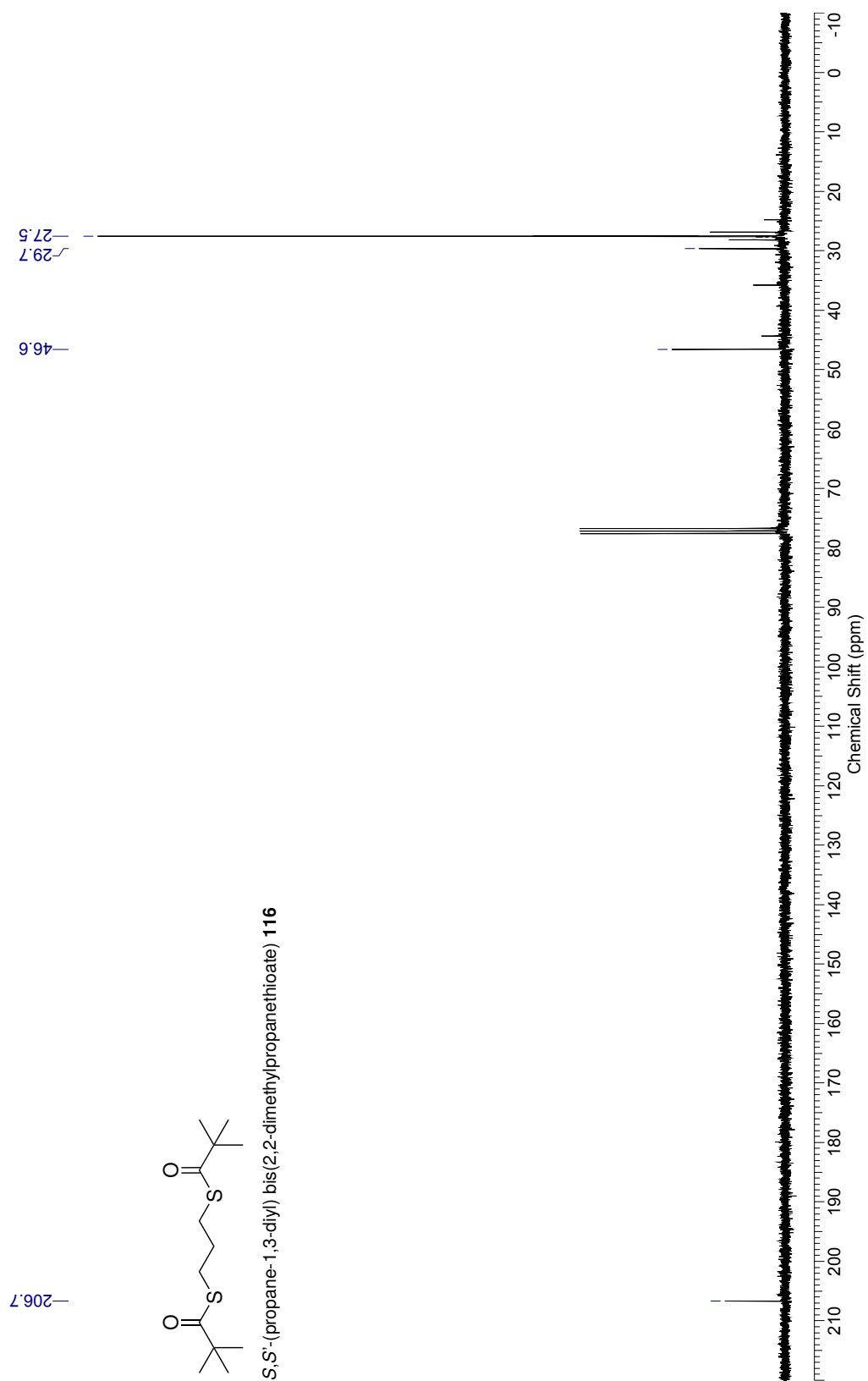
Appendix 29. ^{13}C NMR of compound 109b

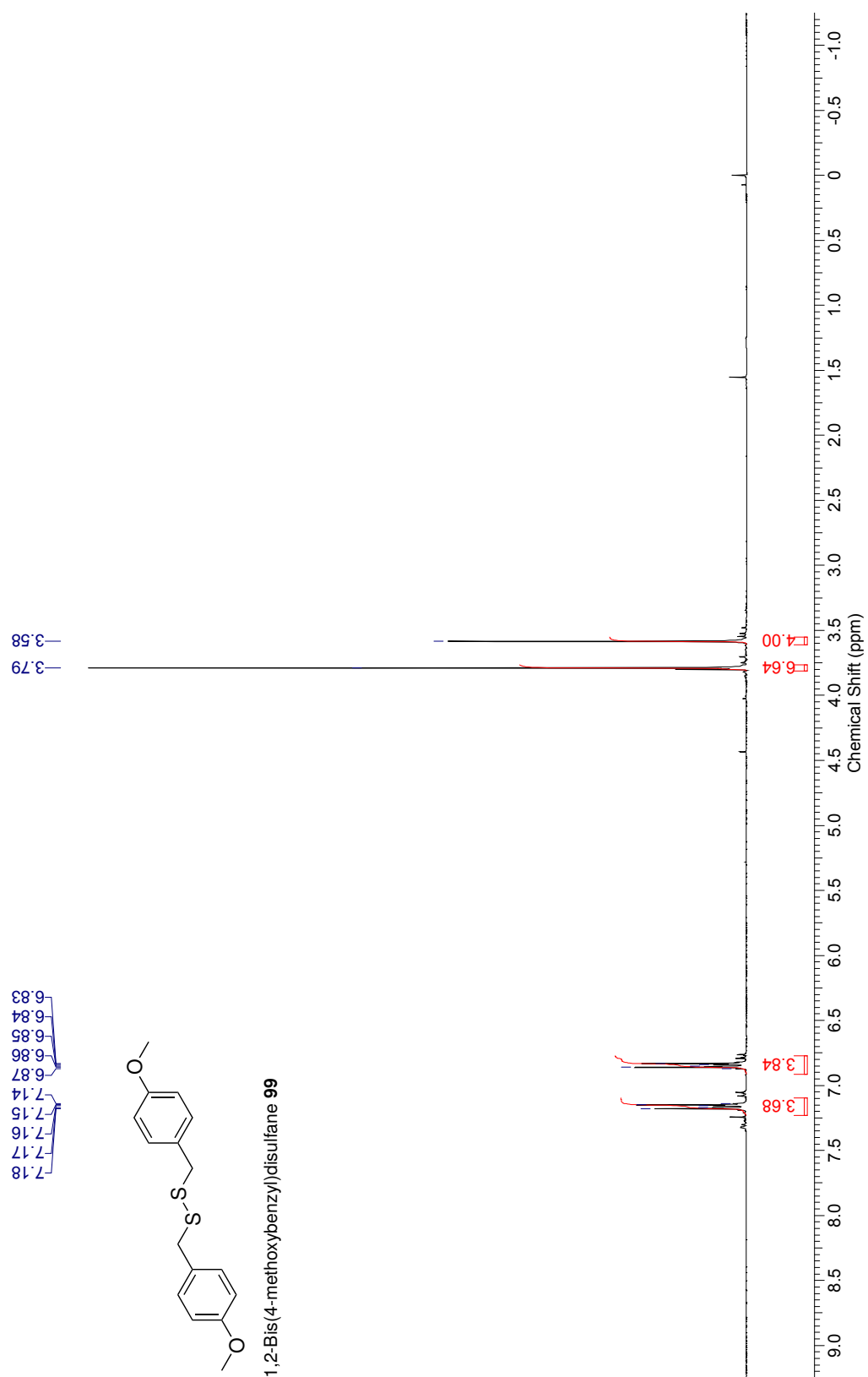
Appendix 30. ^1H NMR of compound 109c

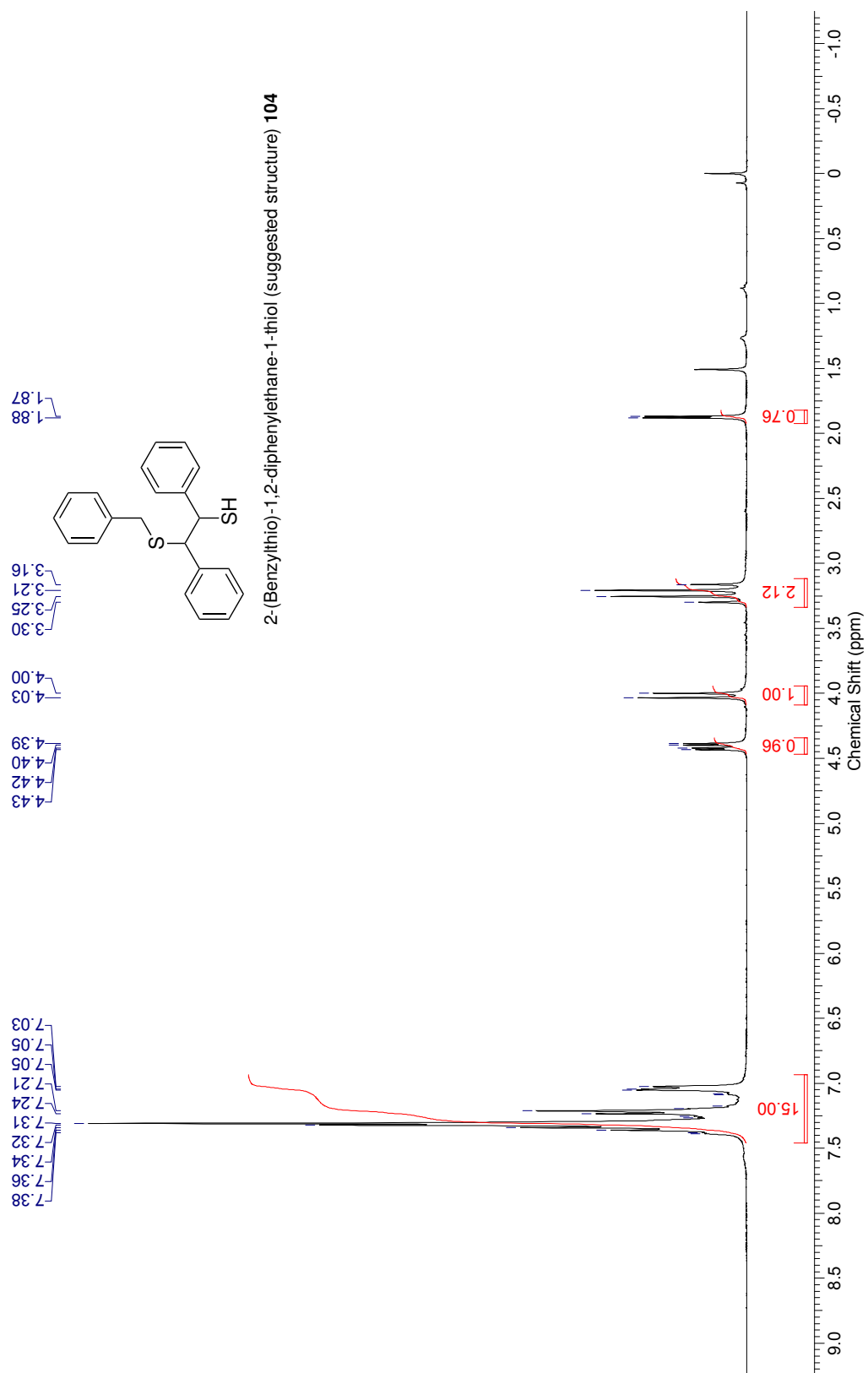
Appendix 31. ^{13}C NMR of compound 109c

Appendix 32. ^1H NMR of compound 110

Appendix 33. ^1H NMR of compound 116

Appendix 34. ^{13}C NMR of compound 116

Appendix 35. ^1H NMR of compound 99

Appendix 36. ^1H NMR of compound 104

Appendix 37. ^{13}C NMR of compound 104